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THÈSE présentée par :

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Régulation de la balance énergétique en conditions environnementales extrêmes : inférence sur la régulation du poids chez l'humain

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"The people that you work with are, when you get down to it, your very best friends."

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« It’s not perfect. It’s life. »

François Péronnet, RACMEM 2022

Ce travail de thèse a fait l'objet des articles, communications orales et affichées suivants :

Articles originaux et revues à comité de lecture international liés au projet de thèse

Bourdier P, Simon C, Bessesen D, Blanc S & Bergouignan A. Role of physical activity in the regulation of body weight: Time to consider light physical activity and sedentary behaviors (2022). 24(2): e13258. Obes Rev.

Bourdier P, Zahariev A, Schoeller D A, Chery I, Le Roux E, Thevenot C, Maillet A, Garnotel M, Gauquelin-Koch G, Bergouignan A, Blanc S & Simon C. Exercise in space: Impact on total energy expenditure, body composition and energy requirements in astronauts onboard the International Space Station (2022) 52(12): 3039-3053. Sports Med.

Bourdier P, Zahariev A, Rudwill F, Kenny H, O'Gorman D J, Chery I, Bareille M P, Gauquelin-Koch G, Normand S, Blanc S, Bergouignan A & Simon C. Resistive exercise combined with vibration training preserve energy balance but is not sufficient to prevent bedrest-induced fat-free mass loss. *En préparation*

Bourdier P, Devitt J, Zahariev A, Chery I, Gallon S, Blanc S, Simon C & Bergouignan A. Physiological adaptations in women during a North Pole expedition – the POWER study. *En preparation*

Articles originaux et revues à comité de lecture international annexes au projet de thèse

Guirado T, **Bourdier P**, Pereira B, Le Roux E, Bergouignan A, Birat A, Isacco L, Thivel D, Duclos M & Metz L. Metabolic profile in women differs between high versus low energy spenders during a low intensity exercise on a cycle-desk (2022) 12(1):9928. Sci Rep.

Bourdier P, Duboz P, Macia E, Ka A, Nazare JA, Cohen E, Boetsch G, Blanc S, Simon C & Bergouignan A. How interdisciplinary research at the crossroad between socio-cultural anthropology, nutritional and physical activity physiology can help addressing the obesity epidemic (2020) 56(1):51-58. Cah. de Nutr. et de Diet.

Le Roux E, Zahariev A, **Bourdier P**, Chery I, Schoeller D A, Maillet A, Thevenot C, Garnotel M, Gauquelin-Koch G, Zwart S A, Smith S M, Van Den Berghe L, Blanc S, Simon C & Bergouignan A. Substrate metabolism and metabolic flexibility in male astronauts onboard the International Space Station: The ENERGY study. *En preparation*

Communications orales

Conférence internationale

Bourdier P, Zahariev A, Chery I, Garnotel M, Maillet A, Thevenot C, Gauquelin-Koch G, Bergouignan A, Blanc S & Simon C. Assessing energy requirements of astronauts onboard the ISS suggests to revisit the exercise countermeasure dogma for planetary exploration – 43rd Committee on Space Research congress, 2021 (Sydney, Australie)

Séminaire

Bourdier P. La dépense énergétique totale et ses composantes : mesures et applications – Ateliers Sciences et Sport, Les webinaires du GDR, 2021 (webinaire)

Conférence locale

Bourdier P. Comment les sciences spatiales nous aident à comprendre le vieillissement humain ? – Jardin des Sciences, Université de Strasbourg, 2022 (Strasbourg, France)

Communications affichées

Conférence internationale

Bourdier P, Zahariev A, Chery I, Bareille M P, Gauquelin-Koch G, Normand S, Simon C, Bergouignan A & Blanc S. Regulation of energy balance during a 21-day bedrest with and without resistive exercise training: the MNX bedrest study – Recent Advances and Controversies in the Measurement of Energy Metabolism congress, 2022 (Québec, Canada)

Conférence locale

Bourdier P, Zahariev A, Chery I, Garnotel M, Maillet A, Thevenot C, Bergouignan A, Blanc S & Simon C. Assessment of energy requirements in astronauts onboard the ISS: Effects of the exercise countermeasure - The ENERGY study – Journées de l’Ecole Doctorale, 2021 (Strasbourg, France)

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Liste des abréviations

Français		English	
AP :	Activité physique	**BM :**	Body mass
AE :	Apports énergétiques	**BMI :**	Body mass index
DE :	Dépense énergétique	**EI :**	Energy intakes
DEAP :	Dépense énergétique induite par l'activité physique	**EE :**	Energy expenditure
DETJ :	Dépense énergétique totale journalière	**FFM :**	Fat-free mass
IMC :	Indice de masse corporelle	**FM :**	Fat mass
MG :	Masse grasse	**ISS :**	International Space Station
MM :	Masse maigre	**PA :**	Physical activity
OMS :	Organisation Mondiale de la Santé	**PAEE :**	Physical activity-induce energy expenditure
MR :	Métabolisme de repos	**PAL :**	Physical activity level
NAP :	Niveau d'activité physique	**TDEE :**	Total daily energy expenditure
TPP :	Thermogénèse post-prandiale		

Dans ce manuscrit, les termes de « masse » et de « poids » désigneront la même variable, à savoir la somme des masses maigres et grasses.

In this manuscript, the terms « mass » and « weight » will describe the same outcome, that is the sum of fat-free and fat masses.

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Personal contribution and impact of COVID-19

This PhD Thesis was conducted from October 2019 to March 2023. Therefore, the sanitary crisis related to the COVID-19 pandemic that started in March 2020 directly impacted this work.

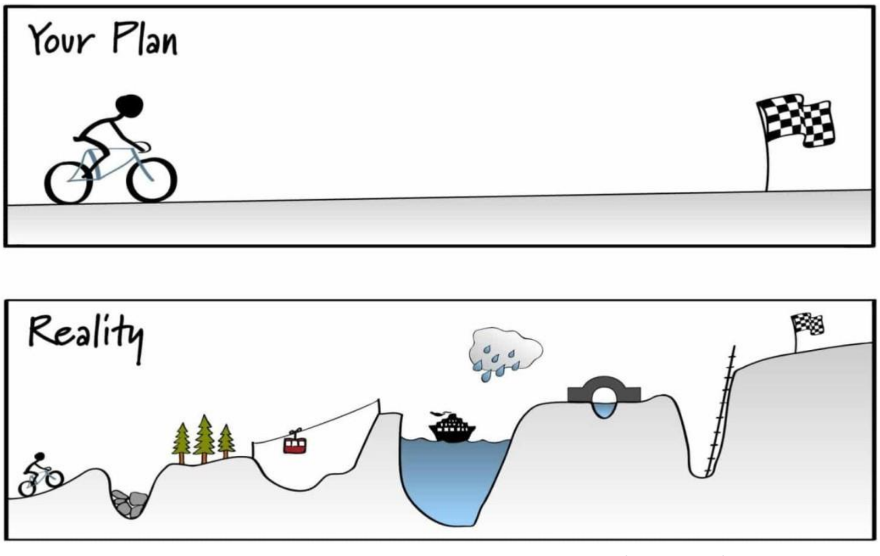
The initial goal of this thesis project was to understand the regulation of total daily energy expenditure (TDEE). In this context, we wanted to test the constrained model (Pontzer, 2015). This model suggests that total daily energy expenditure (TDEE) gradually increases following increases in physical activity (PA), then plateaus above a certain PA threshold due to potential physiological and behavioral compensatory mechanisms. One of the most common explanation concerns a reduction in non-exercise energy expenditure to allow the increase in exercise-induced energy expenditure without exceed the TDEE threshold. This hypothesis may explain how athletes can remain healthy and performant during extreme sport events, or why the effects of PA on weight loss are often limited in people with obesity. To test this model, it was plan to measure TDEE and its components (PA-induced energy expenditure – PAEE, and resting metabolic rate – RMR) combining the use of the doubly labelled water method, indirect calorimetry and accelerometry on models requiring contrasted levels of physical activity in various environments, i.e. the "Marathon des Sables" (250 kms in six stages by running in Moroccan desert), the ENERGY study (astronauts onboard the International Space Station performing daily exercise training as a countermeasure), the POWER study (women reaching the North Pole by ski in full autonomy) and the REMOVE study (aiming to test the effects of cycle desk on metabolic profile and physical fitness from tertiary employees). While data from the ENERGY and POWER have been previously collected by the team, the initial plan was to collect data during the "Marathon des Sables" and the REMOVE study.

After having taken part to the baseline data collection of the REMOVE study in Clermont-Ferrand (France) in January 2020, the national lock-down induced by the COVID-19 sanitary crisis placed the clinical human study on hold for almost a year. The Marathon des Sables, held in Morocco, was also cancelled in 2020 and missions to foreign countries were no longer permitted. Quickly, the plan of the thesis has been adapted and the MNX study (bedrest study aiming to test the effects of a resistive exercise training countermeasure on energy balance regulation) has been included in the thesis to replace the cancelled studies. The inclusion of these new model allowed to investigate the regulation of energy balance in extremely low physical activity level with previously collected data, leading to expand the thesis project to the investigation of energy balance in extreme conditions, and its inference on weight regulation. In the same time, the Doctoral School ED 414 of the University of

Strasbourg allocated me an additional 6-month contract extension to compensate the lockdown-induced delay.

While this thesis uses data previously collected by the team, I had the opportunity to contribute to data collection in the Ferlo (semi-desert sylvo-pastoral, Senegal) in February 2022. This study was part of the TRANSITION project aiming to study the epidemiological transition in a pre-industrial semi-nomadic population, the pastoralist Fulanis, to better understand the respective role of PA, diet, lifestyle and cultures in the regulation of body weight. While this transition happened in Europe in the XXth century, this is currently happening in Senegal. The aim was to measure total energy expenditure and its components, body composition and physical activity pattern in pre-industrial Fulani population living in ultra-rural and remoted environments and compare them to urbanized Fulani from Dakar, an archetype of African urbanization.

As a result of these unexpected global circumstances, my dissertation can be summarized with the figure bellow. The initial plan did not go as smoothly as expected and my opportunities to collect data and samples during clinical human research became limited, I learned resilience, flexibility and adaptability. By using data and analyzing samples previously collected by my research team, and taking advantage of the lock-downs to acquire knowledge in statistical analysis and the use of the SAS software, I was able to develop the skills in data analyses and interpretation, statistical analyses and manuscript drafting. The mission in Senegal also gave me the opportunity to develop skills in data collection on the field in Senegal (remote area, compliance of the participants, mission preparation, etc.), especially using the doubly labelled water and indirect calorimetry.



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Préambule

« I believe every human has a finite number of heartbeats. I don't intend to waste any of mine » Neil Armstrong, first man walking on the Moon

This quote from one of the most famous astronauts can easily be linked to the desire of mankind to discover, reach and conquer new horizons. This is particularly true knowing that only 15% of Earth is habitable on a long-term basis while the 85% remaining are considered hostile with, for example, high and rocky mountains, dry deserts, wet jungles, and oceans. Since the Antiquity and the discovery of the Northern African Coasts, or the first round-world tour by Magellan around 1520, the rapid development of scientific and technological advances offered new perspectives leading to societal progresses with the transfers of plants, animals and culture between the eastern and western hemispheres, but also the mapping of the world and the merge of distant civilizations. This resulted in a better understanding of various scientific aspect too such as biology, astronomy, engineering and others.

Technological advances allowed to travel further and safer with the optimization of navigation systems, ships robustness, adapted clothes and other. However, several expeditions dramatically ended especially in remoted areas where no external assistance was available, with food intakes being lower than expenditures for sustained periods of time, leading to prolonged negative energy balance. Energy balance, that is the tightly dynamic regulated balance between energy intakes and expenditures, is the central determinant of body mass and composition. If some adaptative mechanisms are possible to partially offset the energy deficiency through physiological or behavioral compensations, they might not be sufficient to restore energy balance. However, chronic energy imbalance cannot be sustained indefinitely deleterious consequences such as injury or illness will occur.

The failures of previous missions underlined the central role on nutrition in the maintenance of individuals' health and performance, hence ensure missions success. However, the quantification of food during exploratory missions remains a tricky problem as an overestimation will increase the load to carry and thus the energetic or financial cost to transport it while an underestimation would promote a negative energy balance. The quality of food is also challenging as it requires to provide sufficient macronutrients to individuals, while remaining easy to transport, cook, preserved and tasteful.

Because of logistical and environmental constraints, the maintenance of energy balance in extreme environment remains a vital challenge. This implies to prepare food rations specifically adapted to situations and field constraints, especially in a context where high physical activity-induced energy expenditure is required. A way to approach the effect on physical activity on energy balance regulation is to experimentally vary physical activity-induced energy expenditure from exercise, i.e. from very low to very high level, or other daily spontaneous activities; exercise being a planned and structured form of physical activity. Extreme events such as exploratory missions or adventure in hostile places offer this opportunity as they often require prolonged period of exercise in extreme environments, regarding weather condition or field area. These *in natura* situations compel individuals to cope with the environment (survival, performance / necessary tasks), leading to acute physiological and behavioral adaptations which cannot always be observed in controlled lab settings, particularly in regard to the regulation of energy balance.

With this in mind, this thesis aims to estimate energy requirements of exploratory missions requiring contrasted physical activity levels (i.e. from very low to very high), and the effect of energy balance on body mass and composition changes. The **Chapter 1** will present an overview of the major historic continental explorations that will be followed by a presentation of the main explorations of the 20th century of the Polar Regions and the Space Conquests. These extreme environments are challenging for human exploration and led to various physiological adaptations which are described, along with specific countermeasures used to prevent the deleterious effects of prolonged exposures in polar or spatial environments. Nutrition being one of the determinants of survival and performances maintenance for prolonged missions in extreme environment, **Chapter 2** will present the concept of energy balance and its regulation polar and spatial explorations, underlying the gap in knowledge to fill to ensure the success of the expeditions. Indeed, participants have to face challenging environment which may require high energy turnover when food supply may be limited. After the presentation of the objectives and hypotheses, **Chapter 3** will describe the three models used in this thesis, along with the methodological approach and specific considerations to take into account the characteristics of the models. **Chapter 4** will present results from MNX bedrest study, a ground-based space analog model used to test the preventive effect of a resistive + vibration exercise countermeasure on body composition changes during a 21-day bedrest. **Chapter 5** will present energy requirements and body composition changes of astronauts during long-term mission onboard the International Space Station, assessed during the ENERGY study. **Chapter 6** will use the POWER study to estimate energy requirements of women during a polar trekking, and body composition changes. The last part of this manuscript will discuss the main findings, which will open towards a discussion about the role of physical activity in body mass and composition regulation.

Introduction

Chapitre 1. Les grandes explorations de l’Homme

1. La conquête du monde

L'Homme moderne (Homo Sapiens) est aujourd'hui présent de façon permanente sur la quasi-totalité de la surface continentale de la planète Terre. Depuis son apparition sur le continent africain il y a plus de 200 000 ans, il n'a cessé de dépasser les frontières connues pour conquérir de nouveaux espaces, motivé dans un premier temps par la recherche de nourriture (Marean, 2016). Après avoir conquis l'Eurasie et le sous-continent indien il y a 70-100 000 ans, il s'est dirigé vers l'Océanie 30 à 50 000 ans après. Il y a 25 000 ans, le nord du continent asiatique a été conquis, permettant de rejoindre le continent nord-américain 10 000 ans plus tard et ainsi se répandre rapidement dans toute l'Amérique au cours du millénaire suivant.

Si la survie de la population et la recherche de nourriture ont initié le début des grandes migrations, le désir de découverte et de conquête ont rapidement été un levier majeur dans la découverte de nouveaux environnements. Ainsi, les premières traces de récits exploratoires datant de l'Antiquité décrivent le contour des côtes de l'Afrique occidentale par le carthaginois Hannon Le Navigateur (VI ou VIIème siècle avant notre ère), ou de la Grande-Bretagne par le grec Pythéas. Au cours du XIVème siècle, les motifs économiques et religieux ont conduit les Occidentaux à explorer de nouvelles voies maritimes. Ces expéditions ont notamment permis d'établir de nouvelles voies maritimes permettant de contourner l'Afrique afin de rejoindre l'Asie du sud-est. Le développement des connaissances, notamment géographiques, astronomiques et technologiques, a permis d'entreprendre de nouvelles explorations hors du Monde Connu des européens, qui se résumait jusqu'alors au bassin méditerranéen. Parmi ces avancées scientifiques, les nombreuses avancées techniques et scientifiques développées à la fin du Moyen Âge telles que le principe de la sphéricité de la Terre proposé par Ptolémée en 1406, le développement de la boussole et de l'astrolabe, ou encore l'apparition de la caravelle au Portugal au XVème siècle ont permis de repousser les limites des voyages de l'époque, marquant notamment le passage dans les Temps Modernes. Si de nombreuses explorations se sont succédées en Amérique du Nord au cours des années 1500 suite à sa découverte accidentelle par Christophe Collomb, la seconde étape de la conquête américaine a été initiée par l'ouverture de la Route Maritime des Indes. L'exploration de cette nouvelle voie a poussé de nombreux explorateurs à s'aventurer toujours plus loin, jusqu'à atteindre le Cap de Bonne-Espérance localisé au Sud de l'Afrique en 1487. Ces explorations ont conduit l'équipage de Fernand de Magellan à réaliser le premier tour du monde maritime entre 1519 et 1522. Les nombreuses conquêtes de l'« Âge des Découvertes » ont ainsi permis d'étendre les connaissances du Monde Connu et de réaliser les premières cartes du Monde au début du XVIIIème siècle, avec la totalité des terres émergées cartographiées au XXème siècle.

Si le désir d'exploration a conduit l'Homme à fouler chaque continent, l'environnement (climat, relief) et l'abondance des ressources (naturelles et agricoles) l'ont conduit à s'établir de façon permanente que sur une partie restreinte de la Terre, avec de fortes disparités au niveau de la répartition de la population à l'échelle mondiale (**Figure 1**). Ainsi, seuls 15% de la Terre sont habités par l'Homme, le reste étant considéré comme hostile à la vie humaine (e.g. montagnes, déserts, océans, etc.) (Cotter & Tipton, 2014).

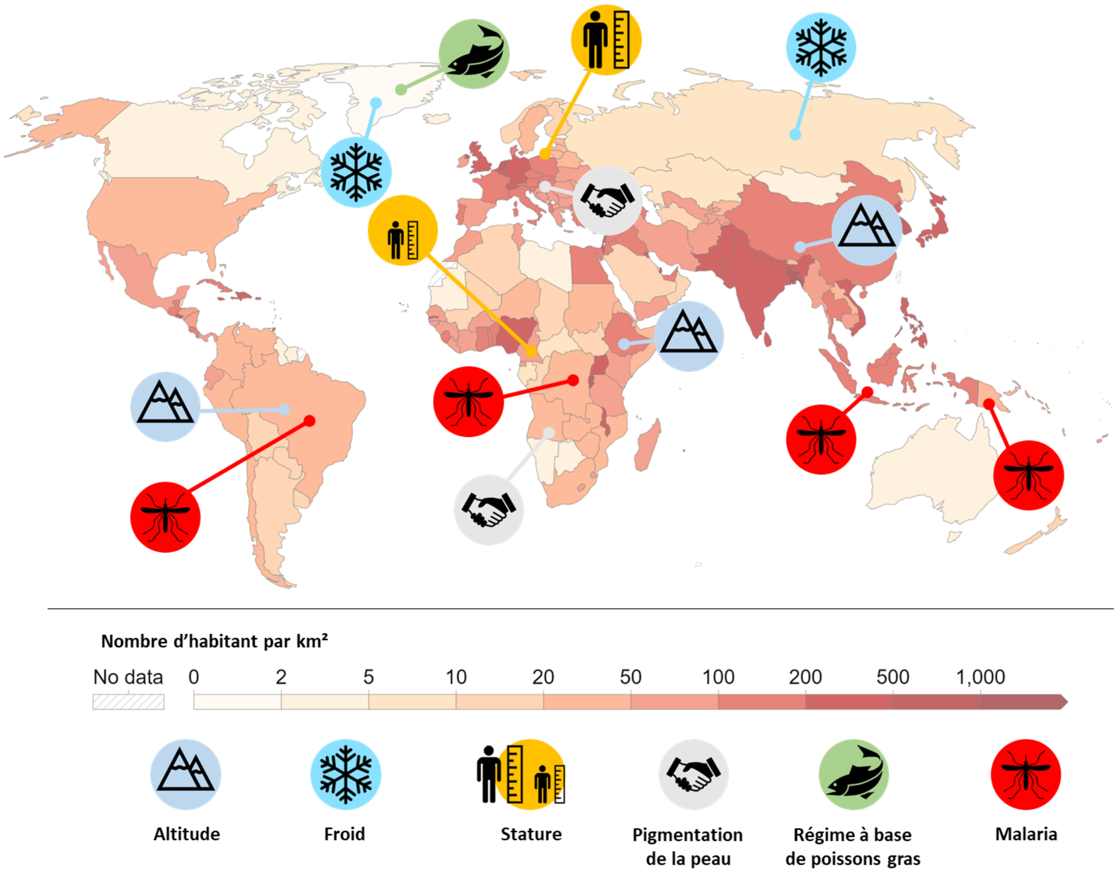


Figure 1: Répartition globale de la densité de la population mondiale en 2021 et des principales adaptations locales à l'environnement.
Adapté de Tishkoff (2015) et Fan et al. (2016).
Source: Our World in Data; Food and Agriculture Organization of the United Nations via World Bank (2021).

Néanmoins, les populations sont exposées à de grandes disparités climatiques et environnementales. A titre d'exemple, environ 17 000 personnes vivent à La Rinconada (Pérou) à une altitude située entre 4 750 et 5 100m, 2 380 000 à Koweït (Koweït) où la température moyenne annuelle est de 34,3°C (max. 51,2°C), et un peu plus de 282 400 personnes habitent à Iakoutsk (Russie) où la température moyenne hivernale est de -40°C (min.-64°C). Ces variations climatiques et environnementales ont conduit à la sélection d'adaptations spécifiques permettant de s'installer de façon globale, en s'adaptant localement (Fan et al., 2016; Tishkoff, 2015). A titre d'exemple, la petite taille des chasseurs-cueilleurs des forêts tropicales d'Afrique, d'Asie et d'Amérique du Sud serait une adaptation induite par des ressources alimentaires limitées, d'une résistance au stress thermique et/ou d'un compromis d'énergie allouée entre le début précoce de la reproduction et l'arrêt de la croissance. La réponse immunitaire pour survivre dans les environnements pathogènes (telle que la malaria transmise par certains moustiques en Afrique sub-saharienne des forêt tropicales), ou encore les niveaux d'hémoglobine pour assurer les fonctions vitales en environnement hypoxique lié à l'altitude rencontrées par les populations des plateaux tibétain, éthiopien ou andin sont d'autres exemples d'adaptations locales induites par l'environnement (**Figure 1**).

Le désir d'exploration étant le propre de l'Homme, de nouveaux défis émergent sans cesse pour repousser les limites logistiques et physiologiques afin d'établir de nouveaux records ou satisfaire une curiosité naturelle, conduisant à s'aventurer dans les 85% restants hostiles. L'époque contemporaine a ainsi été le théâtre d'une nouvelle vague de conquêtes telles que la conquête des airs puis de l'espace moins d'un siècle après, ou encore du Pôle Nord de façon quasi-simultanée (**Figure 2**).

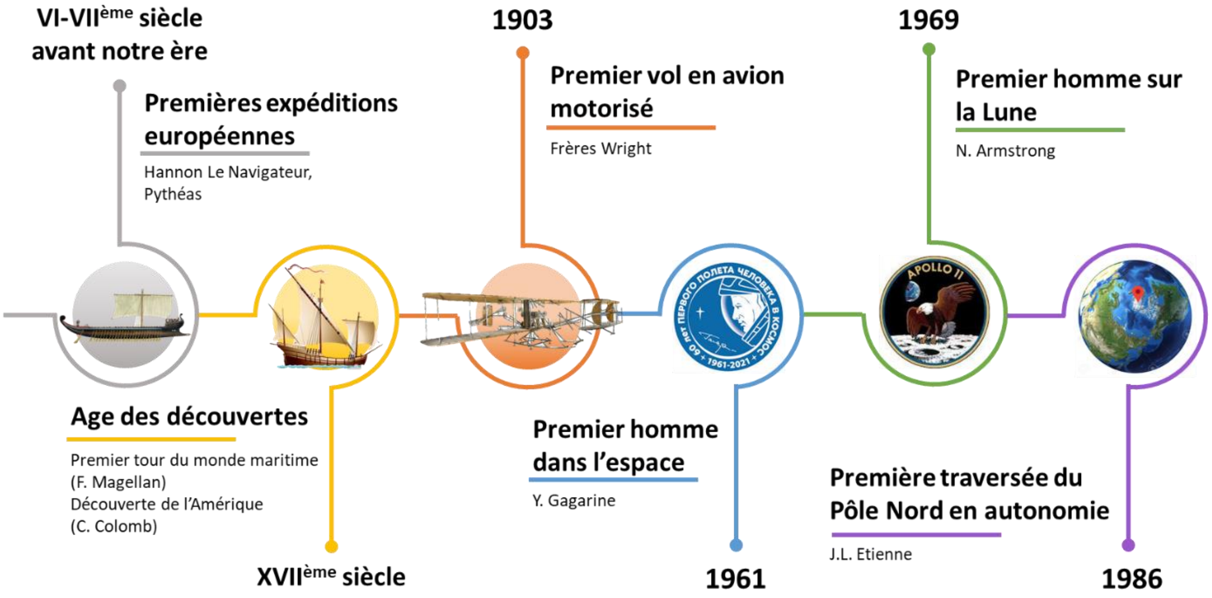


Figure 2: Résumé des principales conquêtes de l'Homme au cours du temps.

Toutefois, le succès de ces conquêtes occulte un grand nombre d'échec. En effet, ces environnements, qualifiés d'« extrêmes » si un ou plusieurs facteurs de stress tels que les flux thermiques, la disponibilité de fluides, la pression de l'oxygène, la pression hydrostatique, la gravité ou encore les polluants sont insuffisants, ou au contraire, en excès (Cotter & Tipton, 2014), vont imposer certains changements structurels et fonctionnels aigus de l'organisme correspondant à l'acclimatation aux contraintes environnementales. Or, la capacité de l'organisme à s'acclimater, soit le processus d'adaptation d'un organisme vivant dans une zone différente de son aire habituelle, à plus ou moins long terme à ces environnements est parfois limitée, ce qui peut mettre en péril le succès de l’expédition et/ou l’intégrité des explorateurs, jusqu’à entraîner leur mort. Il apparaît donc nécessaire de mieux comprendre les altérations induites par ces environnements sur la physiologie de l’Homme. La compréhension des mécanismes adaptatifs, et leurs limites, permettra ainsi de proposer des stratégies adaptées afin de prévenir des altérations induites par l’environnement, notamment dans un contexte où la conquête de nouveaux espaces guidée par des enjeux militaires, scientifiques, sportifs, socio-culturels ou plus simplement personnels poussent les individus à repousser les limites technologiques et physiologiques au quotidien.

Message clé

- Seuls 15% de la Terre sont continuellement habitée par l’Homme, les 85% restants étant hostile à la survie de l’Homme.
- Le processus évolutif a conduit à la sélection d’adaptations spécifiques pour s’adapter localement de façon pérenne dans certaines conditions extrêmes.
- L’organisme peut s’acclimater aux environnements extrêmes auxquels il est confronté et ainsi repousser ses limites afin d’entreprendre de nouvelles conquêtes.

2. Les conquêtes majeures du XXème siècle

2.1. La course au Pôle Nord

De par sa localisation et son climat, le Pôle Nord représente l’un des territoires conquis par l’Homme les plus reculés de la planète, mais également l’un des plus inhospitaliers (Ilardo & Nielsen, 2018). Il y a 5 à 6000 ans, les premières colonies humaines se sont installées autour de la région arctique, dans les actuels Canada et Groënland. Bien que celles-ci aient vécu de façon isolée pendant quatre millénaires, elles ont progressivement disparu et été remplacées par les ancêtres des Inuits il y a 700 ans. Au cours des IX^{ème} et X^{ème} siècles, les raids vikings se sont multipliés dans la région, permettant la découverte de nouvelles terres. L’âge d’or de l’exploration est apparu cinq siècles plus tard, au cours duquel de nombreuses expéditions ont vu le jour, bien qu’accompagnées de nombreux échecs. En 1906, l’équipage européen de Roald Amundsen est le premier à franchir le légendaire passage du Nord-Ouest connectant les océans Atlantique et Pacifique à travers l’archipel canadien. Durant la même période, Frederick Cook et Robert Peary se disputaient la conquête du Pôle Nord. Cook déclara avoir atteint le pôle le 21 avril 1908, tandis que son rival ne l’atteignit qu’un an plus tard. Or, le manque de preuve de Cook ou les données de distance et vitesse fournies par Peary additionnées aux témoignages discordants n’ont permis d’établir la conquête de la latitude 90 à aucun des deux explorateurs. Si la voie terrestre est sujette aux controverses, la conquête par voie aérienne a également été le théâtre de désaccords. Richard E. Byrd et Floyd Bennett ont déclaré avoir survolé le Pôle Nord en 1926, mais les données du journal de bord de Byrd ont conduit à réfuter cet exploit, avec un vol réalisé en parallèle à 100 miles de ce qui était décrit par les deux aviateurs. Ce n'est que le 12 mai 1926 qu'Umberto Nobile et Roald Amundsen survolent le pôle pour la première fois, en fournissant à leur retour des données cohérentes et vérifiées, permettant de leur accorder la première traversée du Pôle Nord. Les développements techniques et technologiques ont par la suite permis de repousser les limites existantes et de nouvelles expéditions ont pu voir le jour, avec la première traversée du pôle à pied (avec des équipages de chiens de traineau et des ravitaillements par largage aérien) en 1969 par l'équipage du britannique Wally Herbert, la première traversée à traineau sans ravitaillement par l'équipage de l'américain Will Steger en 1986 ou encore la première traversée en solitaire sans ravitaillement en 1986 par l'explorateur français Jean-Louis Etienne. Si la conquête des zones polaires a permis à l'Homme de conquérir l'ensemble du globe terrestre, de nouvelles perspectives extra-terrestres ont rapidement émergé.

2.2. La conquête spatiale : la frontière ultime

Voler dans les airs représente l'un des premiers rêves de l'Homme dans son désir de conquête, avec les premières traces de l'Homme-Oiseau observées dans la grotte de Lascaux ont été estimées à 15 000 ans. Si la conquête des airs a été initiée en 855 par Abbas Iban Firnas à bord d'un planneur, les frères Montgolfier sont considérés comme les premiers hommes à voler le 19 septembre 1783. Le premier vol en avion motorisé et contrôlé a été réalisé par les frères Wright 120 ans plus tard, le 17 décembre 1903. Les avancées technologiques ayant stimulées l'esprit d'exploration de l'Homme, la conquête de l'espace apparaît rapidement comme le nouvel objectif à atteindre.

La « course à l'espace » s'est déroulée au cours de la Guerre Froide, avec un premier avantage côté soviétique permis grâce à la réalisation du premier vol habité avec la chienne Leïka le 3 novembre 1957, puis du cosmonaute Youri Gagarine au cours de la mission Vostok-1, le 12 avril 1961, soit 58 ans après le premier vol en avion. Au cours de la décennie suivante, la conquête spatiale a été le moteur d'innovations technologiques permettant aux Etats-Unis ou à l'Union des Républiques Socialistes Soviétiques (URSS) de tenter de se démarquer, jusqu'à ce que les américains Neil Armstrong et Buzz Aldrin soient les premiers à fouler le sol lunaire dans le cadre de la mission Apollo-11 le 21 juillet 1969.

Suite à ces conquêtes phares, l'idée d'une pseudo-installation a rapidement émergé avec la présence continue de l'Homme dans l'espace. C'est dans cette optique que les premières stations spatiales orbitales habitées ont vu le jour avec les programmes Saliout (1973-1991) et Skylab (1973-1979). Si ces stations de type « monolithiques » n'étaient composées que d'un seul bloc, la mise en place des stations de deuxième génération a permis l'ajout de modules supplémentaires, permettant d'augmenter l'effectif des équipages, la durée des missions mais également le développement d'expériences scientifiques liées aux domaines technologiques, physiques ou biologiques. La station Mir est la première du genre. Assemblée entre 1986 et 1996 par l'agence soviétique, la fin de la Guerre Froide et la chute de l'URSS ont permis la mise en place d'une coopération internationale incluant des équipages nord-américains, européens, japonais, indiens ou encore slovaques jusqu'à sa destruction le 23 mars 2001. En 1998 démarre la construction d'un nouveau projet international à l'initiative de onze états Européens, des Etats-Unis, de la Russie, du Canada, du Japon et du Brésil. Il s'agit de la Station Spatiale Internationale (« International Space Station » – ISS), dont la fin est prévue en 2031. Depuis l'Expédition 1 ISS, plus de 260 astronautes issus de 20 nationalités se sont succédés marquant une présence continue de l'Homme dans l'espace depuis plus de 20 ans (Garcia, 2022). Les progrès technologiques et le développement des connaissances en biologie (humaine et végétale), en physique (fluides et matériaux) et technologiques laissent entrevoir de nouvelles perspectives d'exploration, avec un premier vol habité vers Mars fin 2030 – début 2040, ou encore la mise en place du programme Artemis qui permettra à un équipage féminin de fouler première fois le sol de la surface lunaire, et à terme établir une colonie humaine sur la Lune.

Chapitre 2. Le maintien de la balance énergétique : un enjeu de santé et de performance

Le concept de balance énergétique

La balance énergétique est considérée comme un système dynamique ouvert, reposant sur le principal fondamental de la thermodynamique, ou loi de conservation de l'énergie, selon lequel l'énergie ne peut être ni créée ni détruite, mais seulement convertie d'une forme à une autre. Ainsi, l'énergie ingérée (via l'alimentation) devra équilibrer l'énergie dépensée (via les différents postes de dépense énergétique) pour permettre une masse et une composition corporelle stables (**Figure 3**). Dans le cas d'un excès d'énergie, celle-ci serait stockée principalement sous forme de tissu adipeux menant progressivement à une prise de masse grasse, alors qu'un déficit conduirait théoriquement à une déplétion de ces stocks afin de fournir le surplus d'énergie requis (Hill et al., 2012, 2013).

Les apports énergétiques, fournis par l'alimentation, sont constitués des glucides, lipides et protéines ; chaque macronutriment ayant une fonction précise dans le fonctionnement de l'organisme. Le rôle principal des glucides est de fournir de l'énergie aux cellules de l'organisme, les lipides jouent également un rôle de substrat énergétique mais aussi dans la constitution des membranes cellulaires, et les protéines ont un rôle fonctionnel et structurel majeur dans la composition des différentes cellules de l'organisme (Institute of Medicine, 2005) (**Figure 3**). L'apport énergétique est de 9 calories par gramme de lipides et 4 calories par gramme de glucides et protéines. L'alcool apporte 7 calories par gramme.

La dépense énergétique totale journalière (DETJ) est composée du métabolisme de repos (MR), de la thermogénèse postprandiale (TPP) et de la dépense liée à l'activité physique (DEAP) (**Figure 3**). Le MR correspond à l'énergie minimale dépensée par le corps allongé, éveillé et en neutralité thermique. Ainsi, il correspond à l'énergie minimale nécessaire pour assurer le bon fonctionnement des fonctions vitales et est principalement déterminé par la masse métaboliquement active, soit la masse maigre. La TPP correspond à l'énergie nécessaire pour stocker et assimiler les aliments. Enfin, la DEAP correspond à l'énergie dépensée pendant les activités physiques. L'activité physique est définie comme « tout mouvement corporel produit par la contraction des muscles squelettiques qui induit une dépense énergétique [supérieure à la dépense de repos] » (Caspersen et al., 1985). Il est nécessaire de dissocier la dépense énergétique induite par l'exercice structuré (principalement composé d'activités physiques modérées à intenses, 3-6 équivalent métabolique [MET – *metabolic equivalent*) des activités spontanées de la vie quotidienne (principalement composées d'activités physiques d'intensité légère, 1-3METs*)(Ainsworth et al., 2000). La contribution de chacune de ces composantes dans la DETJ est de respectivement 55%, 10% et 35% (la part liée aux activités d'exercice ou spontanée variant selon les individus actifs ou non)(Villablanca et al., 2015).

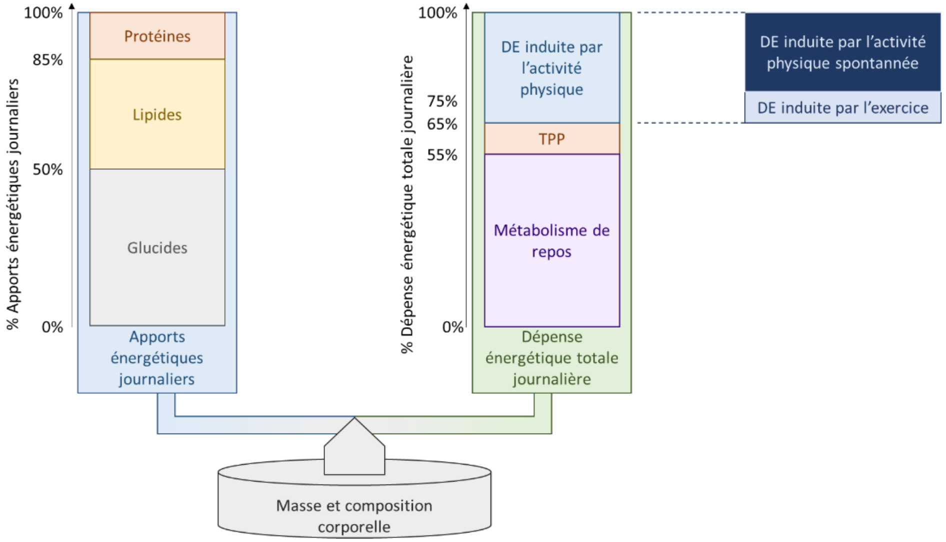


Figure 3: Représentation schématique de la balance énergétique et ses composantes. DE= dépense énergétique ; TPP= thermogénèse post-prandiale.

[*] 1 MET = dépense énergétique de repos (3.5 ml/kg/min O_2 ≈ 1 kcal/g/heure ≈ 0.0042

L’une des adaptations communes aux expositions prolongées aux environnements polaires et spatiaux est une perte de masse corporelle. D’après la première loi de la thermodynamique sur la conservation de l’énergie, une perte de masse ne peut être que le résultat d’une balance énergétique négative prolongée, c’est-à-dire des apports insuffisants pour couvrir les besoins énergétiques liés aux spécificités de l’environnement.

1. Les conséquences d’un déficit énergétique

La relation entre vie, santé et nutrition est connue depuis l’antiquité. Depuis les premières grandes explorations, la question de la quantité de nourriture nécessaire à la survie des équipages est au cœur des préoccupations notamment dans l’hypothèse où les ravitaillements en cours de route seraient impossibles (Tang et al., 2021). Par exemple, les rations des équipages de Magellan lors de son tour du monde étaient principalement composées de fromage, biscuits secs ou autres aliments pouvant se conserver sur des périodes prolongées, et nécessitant peu de transformation (Guillemart, 1890). Or, la qualité des aliments est à prendre en compte puisqu’elle serait à l’origine de maladies comme le scorbut observé chez les marins depuis le XVème siècle. Ainsi, les expéditions de Vasco de Gama et Magellan ont vu mourir 120 (sur 160) et 247 marins (sur 265) sur des voyages d’un a trois ans, respectivement. Ce n’est qu’un siècle plus tard que son développement a pu être prévenu par une supplémentation en jus de fruits de type citrus (citron, pamplemousse, orange, etc.) basée sur une connaissance empirique des marins, et au XXème siècle que la carence en vitamine C est reconnue comme cause du scorbut.

Cet exemple souligne l’importance de la nutrition dans le succès des grandes explorations, ou des missions prolongées. Or, les facteurs logistiques (impossibilité de ravitaillement, masse additionnelle à transporter, préservation), économiques (coût des rations, quantité adaptée) et qualitatifs (composition des aliments) imposent d’estimer au plus juste les besoins des individus en prenant en compte les spécificités de l’environnement et des activités des individus. Or, une non-adéquation entre les besoins et les apports entraînent un déséquilibre de la balance énergétique a été couramment observé au cours de séjours prolongés en milieu hostile (Halsey & Stroud, 2012; Pasiakos, 2020). Celui-ci se traduit par une perte de masse corporelle et une altération de la composition corporelle. Or une balance énergétique prolongée et une restriction calorique marquée peuvent entraîner des conséquences néfastes sur les performances et la santé des individus, ainsi que le succès de la mission (Bergouignan et al., 2016; Pasiakos, 2020). Ainsi, une balance négative prolongée est associée à une altération de la masse et de la fonction musculaire et une déplétion des stocks énergétiques (tissu adipeux, foie, muscles), ou encore une déshydratation qui favorisera l'altération des performances et ultimement mettra en péril la survie (Carbone et al., 2012; Hill et al., 2012; Pasiakos, 2020).

Si la régulation de la balance énergétique à travers la quantité de nourriture adaptée est considérée comme un élément important depuis plusieurs siècles, elle bénéficie aujourd'hui d'un intérêt majeur dans la planification des futures missions de l'Homme comme la colonisation de la Lune ou la conquête de Mars par les Agences Spatiales, le succès des opérations militaires en milieu hostile ou la réussite d'évènements d'ultra-endurance où les individus doivent composer avec des ressources limitées dans des environnements requérant un niveau de performance élevé durant de longues périodes. Toutefois, la quantification optimale des apports impose de prendre en compte les spécificités de la mission liées à l'environnement ou aux tâches spécifiques impliquant des niveaux d'activité physique plus ou moins élevés.

2. L'environnement polaire

2.1. Adaptations physiologiques à l'environnement polaire

Cinq composantes principales ont façonné la Vie sur Terre dont l'Homme depuis des milliers d'années, à savoir la gravité, l'oxygène, la lumière solaire, la pression atmosphérique et les conditions climatiques. Ces différentes pressions environnementales ont permis de sélectionner des adaptations permettant la vie dans des environnements aux conditions parfois extrêmes (Fan et al., 2016). L'étude de l'Homme dans ces environnements extrêmes (zones polaires, déserts, montagnes, etc.) permet de comprendre, de façon accélérée, comment sont mis en place les mécanismes d'adaptation biologiques et physiologiques, mais également cognitifs et psycho-sociaux ayant permis à l'Homme de conquérir le monde. Le Pôle Nord est un environnement extrême dont la traversée est composée de défis logistiques, physiologiques et psychologiques. Le climat va représenter le principal enjeu, puisque les très basses températures (moyenne : -34°C), le vent et la faible humidité vont avoir une influence considérable sur le maintien des performances physiques et cognitives (Færevik et al., 2013). Les atteintes les plus répandues suite à une exposition prolongée au froid extrême sont une altération fonctionnelle des extrémités altérant la dextérité et l'équilibre, favorisant le risque de chutes et de blessures, mais également des douleurs voire des engelures localisées ainsi que des atteintes psychologiques (baisse de la vigilance et de la concentration, et stress) (Holmer, 2009).

En particulier, l'exposition prolongée au froid s'accompagne d'une perte de fluide corporelle représentant une déshydratation de 2 à 5% de la masse corporelle (O'Brien et al., 1996). Celle-ci peut s'expliquer par une diurèse accrue, une diminution de la sensation de soif et donc des apports hydriques ou encore d'une transpiration excessive suite aux exercices intenses dans les combinaisons hivernales (Kenefick et al., 2004). Cette hypo-hydratation va avoir un effet néfaste sur le cœur en augmentant le travail cardiaque, favorisant une fatigue précoce et des performances réduites (Watanabe et al., 2020). De façon plus générale, le froid polaire peut compromettre le maintien de la balance thermique, qui consiste à maintenir une température corporelle interne entre 36.5°C et 37.5°C. En effet, le froid est associé à une augmentation de la température périphérique cutanée et des pertes de chaleur dans l'environnement, résultant en une baisse de la température corporelle interne. Une balance déséquilibrée peut être à l'origine d'une hypothermie modérée à sévère (-1 à -4°C de température corporelle), et entraîner des réponses plus ou moins importantes selon le stade d'hypothermie (Leon et al., 2011). Si la température interne passe en dessous de 35°C, les fonctions cérébrales vont être détériorées, dû à un changement de pH induit par le ralentissement des réactions cellulaires chimiques. Ces altérations cérébrales peuvent être à l'origine d'une altération de la coordination motrice et d'une confusion, favorisant le risque de blessure. Si la température chute en dessous de 34°C, les dommages vont être amplifiés, avec comme réponse ultime la mort (Askew & Hecker, 1989), nécessitant ainsi la mise en place de mécanismes intrinsèques et de stratégies extrinsèques pour maintenir la neutralité thermique (Kingma et al., 2012).

2.2. Les stratégies de lutte contre le froid et leur impact énergétique

La traversée du Pôle Nord représente un véritable challenge physiologique au niveau énergétique liés à la locomotion et la lutte contre le climat, dont les premières explorations se sont soldées par des altérations de la santé allant jusqu'à la mort en raison d'une méconnaissance du coût énergétique d'un tel périple (Halsey et al., 2015). En effet, les explorateurs, en plus de la locomotion à pied ou à ski dans un environnement dont les contraintes climatiques et géographiques s'avèrent contraignantes, sont amenés à transporter leurs propres réserves alimentaires et autres équipements, tout en cherchant à limiter les pertes de chaleur et maintenir une neutralité thermique (Halsey & Stroud, 2012).

2.2.1.Les mécanismes intrinsèques de la régulation thermique

La vasoconstriction des vaisseaux périphériques est le premier processus de régulation de la chaleur permettant de réguler la température cutanée lorsque la température corporelle passe de 37 à 35°C.

Si celle-ci ne suffit pas à prévenir les pertes de chaleur et que la température corporelle tombe à 34°C, le « pré-frisson » puis le frisson thermique vont être stimulés (Armahizer et al., 2020). Au cours d'une contraction musculaire, un quart de l'énergie est utilisée pour produire le mouvement, alors que le reste est dissipée sous forme de chaleur. Ainsi, l'intensité du frisson (pourcentage de la force maximale volontaire du muscle) va augmenter de façon quasi-linéaire en fonction de la température cutanée, induisant une augmentation de la dépense énergétique allant jusqu'à 4.2 fois le MR (Haman & Blondin, 2017; Nimmo, 2004). Or, le frisson thermique est également associé à une vasodilatation des artérioles irriguant le muscle squelettique, réduisant l'isolation.

Si le frisson ne suffit pas, d'autres mécanismes peuvent être stimulés par le froid afin d'agir sur la thermogénèse, notamment via l'activation du tissu adipeux brun (TAB). Le TAB est un organe thermogénique dont l'activation permet d'augmenter la production de chaleur en réponse à un stimulus froid afin de maintenir la température corporelle sans avoir recours au frisson (Kulterer et al., 2020a; Saito, 2013). S'il a longtemps été pensé que le TAB était spécifique aux petits mammifères et nouveau-nés, de nouvelles évidences ont démontré sa présence chez l'adulte et son implication dans la régulation de la thermogénèse et de la dépense énergétique totale journalière (DETJ) (Nedergaard et al., 2007). Ainsi, le froid va activer le système nerveux sympathique qui va stimuler la libération de noradrénaline. Celle-ci va se fixer sur les récepteurs β-adrénergiques et initier une cascade de réaction résultant en l'hydrolyse des triglycérides stockés dans le TAB. Les acides gras relâchés vont ainsi être oxydé pour produire de l'énergie qui sera dissipée sous forme de chaleur (Saito, 2013). Le froid va également stimuler la mobilisation du tissu adipeux blanc (forme de tissu majoritaire chez l'adulte) et conduire à la mobilisation des stocks de tissu adipeux pour fournir de l'énergie via l'oxydation des lipides, bien que sa contribution soit moins importante que celle du TAB. Ainsi, les individus avec un TAB métaboliquement actif parviennent à maintenir un température cutanée stable au détriment d'une augmentation de la DETJ. A l'inverse, les individus dont le TAB est indétectable (estimé par la capacité du TAB à absorber le traceur ^{18}FDG mesurée par PET/CT scan) maintiennent une DETJ stable mais voient leur température cutanée diminuer. A titre d'exemple, une exposition de deux heures en sous-vêtements dans une pièce à 19°C est associée à une faible baisse de la température cutanée (-0.14°C) et à une augmentation de la dépense énergétique au repos de 1.7 MJ/jour chez les individus avec un TAB métaboliquement actif alors que ceux avec un TAB indétectable par imagerie ont vu leur température cutanée diminuer de 0.60°C sans impacter la dépense énergétique au repos (Yoneshiro et al., 2011). S'il n'a jamais été mesuré, son impact énergétique au cours d'une exposition prolongée à de très basses températures comme celles rencontrées en milieu polaire pourrait être encore plus important. En effet, une relation négative a été observée entre le frisson (en pourcentage de la contraction maximale volontaire) et le volume de TAB, confirmant le rôle complémentaire de ces deux processus adaptatifs de lutte contre le froid. Ainsi, Ouallet et al. ont observé chez six hommes adultes que la dépense énergétique de repos augmentait d’1.8 fois et la température cutanée diminuait de 3.8°C sans changement de la température interne après une exposition de 3h en milieu froid (≈18°C de façon à ne pas induire de frisson thermique) (Ouellet et al., 2012).

2.2.2.Les stratégies extrinsèques de la régulation thermique

Si ces deux principales régulations sont stimulées de façon involontaire, il est possible de moduler la température corporelle par d’autres stratégies. La plus courante repose sur l’utilisation de vêtements spécifiques dont les progrès techniques et technologiques constants permettront de limiter les pertes de chaleur liées au froid.

La technique la plus répandue repose sur un système de multicouche (minimum 3) où les deux premières couches jouent un rôle majeur dans l’isolation de la production de chaleur corporelle afin d’éviter des perte trop importantes et l’évacuation de l’humidité, tandis que la couche externe a pour fonction de fournir une protection contre l’environnement (vent, pluie), sans compromettre les fonctions des deux premières couches (Færevik et al., 2013). Toutefois, ces tenues lourdes et encombrantes peuvent impacter la performance des individus en augmentant la contrainte musculaire, et la charge de travail via une altération de l’efficience locomotrice (Holmer, 2009). A titre d’exemple, l’équipement spécifique des militaires évoluant en milieu froid à très froid est estimé au minimum à 19kg, contre 17kg initiaux requis en milieu tempéré (comprenant le casque et le gilet pare-balle) (McCarroll et al., 1979). Cette charge additionnelle est associée à un cout énergétique supplémentaire de 8% comparativement au port de la tenue requise en milieu tempéré, et les effets d’obturation et de friction des vêtements multicouches et des chaussures spécifiques pour temps froid peuvent induire une dépense énergétique supplémentaire de 16% (Teitlebaum & Goldman, 1972). Cela se traduit par des dépenses énergétiques moyenne allant jusqu’à 22.6 MJ/jour (soit 2.8 fois leur métabolisme de repos théorique) mesurées au cours d’un entraînement de terrain de 10 jours en milieu froid (-10 à 5°C), contre 17 MJ/jour pour le même entraînement au même endroit (Quantico, Virginie, Etats-Unis) en température modérée (9 à 31°C). Ces dépenses élevées sont notamment dues au tractage de charges lourdes, et aux longues périodes passées en activité physique intense (Hoyt et al., 2001; Tharion et al., 2005).

La nutrition est également une stratégie puisque la modification des aspects qualitatif et quantitatif jouera un rôle clé dans la thermorégulation à travers la régulation de la balance énergétique. L’un des premiers mécanismes modulables volontairement par les individus peut être de créer une balance énergétique positive dans laquelle les apports seront supérieurs aux dépenses, où l’excès d’énergie sera stocké majoritairement sous forme de tissu adipeux (Hill & Peters, 2013), ce dernier étant positivement associée à l’isolation des tissus, et donc limite les pertes de chaleur de l’organisme (DeGroot et al., 2006; Hayward & Keatinge, 1981). Si la quantité apparaît comme le principal déterminant, la qualité doit également être considérée avec attention. Ainsi, la composition des apports énergétique peut également être modulée afin d’agir sur la production de chaleur via les mécanismes de thermogénèse post-prandiale, puisque le contenu énergétique de l’aliment sera l’un des principaux déterminants de la TPP. La TPP peut ainsi augmenter la dépense énergétique de 10 à 15% (voire jusqu’à 26% de façon aigue), celle-ci étant positivement associée à la température cutanée (Kingma et al., 2012; Westerterp-plantenga et al., 1990; Westerterp, 2004). En effet, la consommation de lipides contribue de 0 à 3% de la TPP, les glucides de 5 à 10% et les protéines de 20 à 30% (tandis que l’alcool contribue de 10 à 30% de la TPP), les régimes avec une proportion élevée de protéines induisant par conséquent une TPP plus importante que des régimes iso énergétiques riches en lipides (Martens et al., 2015; Westerterp et al., 1999).

2.3. Des apports énergétiques inadaptés aux conditions polaires

En plus des dépenses énergétiques importantes allant de 16 à plus de 25 MJ/jour induites par les mécanismes cités précédemment, il est nécessaire de prendre en compte les apports énergétiques qui sont la plupart du temps, limités en raison des contraintes logistiques (rations pré-emballées, impossibilités de ravitaillement durant la mission, prolongation involontaire du temps d’expédition) (Ahmed et al., 2020). De plus, une baisse spontanée de la prise alimentaire a été observée en raison de la baisse de palatabilité / variété des aliments, des difficultés liées à la préparation des repas ou d’une volonté d’économiser les rations résultant en une anorexie volontaire à l’origine d’altérations physiologiques et psychologiques pouvant mettre en péril le succès de la mission et les performances des équipes. Ainsi, des enquêtes et questionnaires ont montré que les apports des soldats ne couvraient que 61 à 70% des besoins énergétiques au cours d’un entraînement de terrain de 3 à 10 jours, menant à une perte de poids inférieure à 2% de la masse corporelle initiale, sans changements significatifs de la composition corporelle (Johnson et al., 2018; Jones et al., 1993). Toutefois, un rapport de l’armée américaine a décrit que les soldats ne déclaraient consommer que 25% de leurs dépenses (mesurées par la technique de l’eau doublement marquée) après un entraînement de terrain de 10 jours en milieu froid (-5°C à +5°C), bien que les apports soient probablement sous-reportés par les soldats (Hoyt et al., 2001). Ce déséquilibre de la balance énergétique était à l'origine d'une perte de masse corporelle de 4% malgré la disponibilités de rations militaires dont le contenu énergétique était basé sur les besoins théoriques (Hoyt et al., 2001).

Bien qu'un grand nombre de données ait été collectée sur la régulation de la balance énergétique dans des modèles spécifiques tels que les militaires ou des athlètes entraînés aux expéditions en condition extrême (Charlot, 2021; Charlot et al., 2020; Hattersley et al., 2020; Paulin et al., 2015), très peu d'entre elles se sont intéressées à la population générale. Si certaines études ont mesuré la DETJ et les apports avant et après une expédition polaire ainsi que les changements de composition corporelle (Hattersley et al., 2019a), aucune étude n'a à ce jour mesuré spécifiquement les besoins énergétiques de femmes non-athlète au cours d'une expédition polaire, ou la régulation de la balance énergétique de façon plus globale, limitant ainsi la généralisation des résultats. A titre d'exemple, des données issues de courses de longues distance (>100km en course à pied) ont permis de mettre en avant une perte de force des extenseurs du genou moins importante chez les femmes comparativement aux hommes (Besson et al., 2021), ou encore une différence dans l'oxydation des substrats énergétiques entre des femmes et des hommes non-athlètes (avec une oxydation plus importante des lipides chez les femmes comparativement aux hommes) (Cano et al., 2022). Ces données soulignent l'importance de conduire des études chez les femmes afin d'étudier leurs spécificités dans une optique d'optimisation de la performance et / ou de la santé.

Messages clé

- Le Pôle Nord représente l'un des territoires conquis par l'Homme les plus reculés de la planète.
- Son environnement (froid extrême, vent, topographie) va être à l'origine d'adaptations physiologiques dont les conséquences sur la santé et les performances peuvent être délétères, voire dramatiques.
- Bien que les apports énergétiques soient théoriquement calculés pour couvrir les besoins énergétiques, une balance énergétique négative est couramment observée au cours des expositions prolongées en milieu polaire impliquant des niveaux d'activité physique importants.
- Très peu de données existent sur les besoins énergétiques des femmes en environnement polaire. Aucune d'elle n'a étudié la régulation de la balance énergétique dans une population non-athlète.

3. L’environnement spatial

3.1. Les adaptations physiologiques à la microgravité

L’adaptation à la microgravité représente un véritable enjeu en termes de santé et de performance puisque la biologie de l’Homme, comme celle des autres êtres vivants et notamment les vertébrés, a été naturellement sélectionnée dans un environnement à 1G (≈9.81 m/s^2). Or, la gravité à bord de l’ISS est proche de 0G, tandis qu’elle est de respectivement 0.12G et 0.38G sur la Lune et Mars (1.21m/s^2 et 3.72m/s^2). Ainsi, la microgravité rencontrée par les astronautes au cours des vols spatiaux va être à l’origine de nombreuses altérations, impactant la quasi-totalité des systèmes physiologiques (e.g. musculosquelettique, cardiovasculaire, hormonal, neuro-vestibulaire) mettant ainsi en péril les performances et la santé des équipages, voire le succès des missions (Vernikos, 1996).

3.1.1.Fluides corporels et système cardiovasculaire

Au cours des premières heures en microgravité, les astronautes doivent faire face à la redistribution des fluides corporels (Drummer et al., 2000; Hargens & Richardson, 2009). La disparition de la gravité terrestre va induire un changement de gradient de pression au cours duquel les fluides répartis au niveau du membre inférieur (environ 2 litres) sont redistribués au niveau thoraco-céphalique à l’origine des phénomènes de « puffy face » et de « chicken legs » (Aubert et al., 2016). Au niveau fonctionnel, ce changement de gradient va entraîner une migration des fluides intravasculaires vers l’espace extracellulaire à l’origine d’une hypovolémie de 10 à 15% du volume sanguin. Cette dernière va entraîner des réponses physiologiques adaptatives telles qu’une augmentation du débit cardiaque de 20 à 40%, une diminution du volume d’éjection systolique de 35 à 46% ou à une diminution de la pression artérielle (Baran et al., 2021; Norsk et al., 2015). La redistribution des fluides corporels dans la partie supérieure du corps va également induire une hypoperfusion cérébrale à l’origine d’une intolérance orthostatique, et d’une augmentation de la pression intracrânienne (Jirak et al., 2022). Ces altérations fonctionnelles vont stimuler la mise en place d’adaptations structurelles, avec notamment un remodelage caractérisé par une augmentation de la sphéricité du muscle cardiaque ou une augmentation de la distensibilité artérielle au niveau de la carotide (Hughson et al., 2016; Summers et al., 2010). Ces altérations du débit cardiaque sont à associer à une diminution de la différence artérioveineuse (i.e. différence entre le contenu en oxygène des artères et des veines), résultant en une diminution de la consommation maximale d’oxygène (VO_2max) de 20%, mettant en péril les performances cardiovasculaires des astronautes, mais également leur santé (Ade et al., 2017) (**Figure 4**).

3.1.2.Système musculaire

Les vols spatiaux vont également supprimer la contrainte gravitationnelle qui agissait sur les muscles posturaux. L'activité locomotrice va chuter en vol, plaçant ainsi les astronautes dans une situation d'hypodynamie et hypokinésie, au cours de laquelle les stimulations du système musculosquelettique vont chuter (Stein, 2013). Les forces de réaction à bord de l'ISS sont également réduites de 65 à 77% entre les activités de squat et de marche (Genc et al., 2010). Ainsi, une perte de masse musculaire induite par la microgravité a été couramment observée depuis les missions Gemini, Soyouz ou Skylab (Convertino, 1990). Ces altérations constituent un véritable enjeu opérationnel et médical puisqu'elles peuvent mettre en péril les performances mais également la santé des membres des équipages. Ainsi, les données collectées sur Mir ont observé une baisse quasi-identique entre la densité minérale osseuse totale et la masse maigre (-3.4 et -3.5%, respectivement), principalement localisées au niveau du membre inférieur (LeBlanc et al., 2000b).

Plus spécifiquement, les adaptations musculaires à la microgravité peuvent être étudiées à des échelles variées, allant de la myofibrille et des réactions chimiques nécessaires aux mécanismes de contraction (e.g. cycle du calcium, fonctionnement mitochondrial, etc.) à la surface de section transversale et la production de force. D'un point de vue fonctionnel, une relation entre perte de masse / force et durée de vol a été observée sur les fléchisseurs et extenseurs du genou, et les fléchisseurs plantaires, ainsi qu'une altération du profil force-vitesse, témoin privilégié de la fonction musculaire (Adams et al., 2003). Les données issues des missions Skylab ont mis en évidence une diminution du volume du membre inférieur de 7 à 10%, initiée la perte de fluides corporels, et amplifiée par l'inutilisation des muscles. Au cours des missions de plus longues durées telles que celles sur Mir, une perte significative du volume musculaire a été observée, avec une diminution du volume de 20 à 24% des muscles de la jambe, et 12 à 16% des muscles de la cuisse (LeBlanc et al., 2000a). Des données similaires ont été observées sur des missions réalisées à bord de l'ISS (6 mois) avec des pertes moyennes de -10 à-19% des muscles de la jambe et -7 à -4% pour les muscles de la cuisse, tandis qu'aucun changement n'a été observé pour les muscles des bras (Gopalakrishnan et al., 2010). Les données collectées au cours des différentes missions ont montré une perte de masse musculaire moyenne de 0.57% par mois, avec de fortes disparités régionales entre les membres supérieurs (-0.0 [SD 0.8]%) et inférieurs (-1.0 [0.7]%), avec un plateau à partir de 270 jours lorsque la masse musculaire atteint 70% des valeurs pré-vol (Comfort et al., 2021; di Prampero & Narici, 2003). Ces différences au niveau des atteintes peuvent s'expliquer par la typologie des groupes musculaires concernés; les fibres de type II (majoritaires dans les muscles de la jambe) étant plus sensibles à l'atrophie induite par la microgravité que les fibres de type I (majoritaires dans les muscles de la cuisse), probablement en raison de leur épaisseur plus élevée au sol (Fitts et al., 2000). Il a été reporté qu'un vol de 11 jours induisait une diminution de la proportion de fibres de type I de 6 à 8%, dû à une augmentation de la proportion de fibres de type IIA (aucun changement apparent de la proportion de fibres de type IIB). Or l'atrophie musculaire, bien que visible sur chaque type de fibre, est plus importante sur les fibres de type IIB, puis IIA et enfin I dans le vastus lateralis (Edgerton et al., 1995). Cette atrophie musculaire pourrait s'expliquer par un turnover protéique accéléré résultant en une balance azotée négative. Toutefois, ce stress apparaît au cours de la première dizaine de jours en vol, puis se stabilise lors des missions prolongées, grâce à une adaptation de l'organisme (Stein et al., 1996; Stein et al., 1999a). Ces changements structurels s'accompagnent de changement fonctionnels, résultant en une perte de force et d'endurance musculaires (Comfort et al., 2021; Fitts et al., 2001; Gopalakrishnan et al., 2010) pouvant mettre en péril le succès de la mission mais également la santé des équipages au cours de missions prolongées (Ryder et al., 2013). Bien qu'une grande variabilité ait été observée au cours des missions, des tests ou des astronautes, les muscles des composés majoritairement de fibres de type I présentent des pertes de force plus importantes que les muscles avec un pourcentage élevé de fibres de type II (Comfort et al., 2021). Ces altérations structurelles sont à l'origine de pertes de force allant de 9 à 11% selon les groupes musculaires étudiés et de 16% d'endurance au cours des vols en navette de 5 à 17 jours, tandis que des pertes moyennes de l'ordre de 10 à 28% de la force initiale, et de 14% de l'endurance musculaire ont été mesurées après 6 mois à bord de l'ISS (Gopalakrishnan et al., 2010) (**Figure 4**). Néanmoins, une grande variabilité inter-individuelle a été reportée par les investigateurs des différentes études, notamment en raison i) de la faible taille des échantillons liée aux contraintes logistiques des études spatiales et ii) des caractéristiques différentes propres à chaque astronaute.

3.1.3.Système squelettique

De façon conjointe à la perte de masse musculaire, une perte de masse osseuse est couramment observée chez les astronautes. Le système osseux est le résultat d'une balance dynamique entre les activités de résorption et de formation osseuse. La résorption étant un processus continu, les stimulations notamment à travers les chocs ou la tension induite par la contraction musculaire vont stimuler l'activité de formation (Bettis et al., 2018). La microgravité va diminuer drastiquement les stimuli nécessaires à la formation, résultant en une balance négative à l'origine d'une perte de densité minérale osseuse en vol, et qui persiste après le retour sur Terre. Au cours des missions dans le cadre du programme Gemini, une perte de densité minérale osseuse de 3 à 23% a été observée, bien qu'une erreur de mesure de 7% ait été reportée par la suite en raison de difficultés techniques et méthodologiques (Mack & LaChance, 1967; Vose, 1974). Au cours de missions de plus longues durées telles que le programme Skylab (84 jours), une perte de densité minérale osseuse de l'ordre de 11% a été observée (Smith et al., 1977). Les techniques d'absorptiométrie simple utilisées au cours des missions Gemini, Apollo ou Skylab ont laissé place aux mesures de DEXA (« dual X-ray absorptiometry »), utilisé de nos jours en routine chez les astronautes a minima avant et après la mission (Vico & Hargens, 2018). Si les mesures par imagerie médicale demeurent difficiles du fait des contraintes en vol, les prélèvements d'échantillons biologiques (i.e. sang, urine) permettent de doser des marqueurs de résorption ou de formation osseuses. Au cours de Skylab (84 jours), une balance calcique négative de 300 mg/jour a été observée, ainsi qu'une augmentation des marqueurs urinaire de résorption osseuse (« collagen cross-link » : NTX, PYD, DPD) (Smith et al., 1998; Thornton & J.A., 1977). Des résultats similaires ont été observées au cours de missions sur la station Mir (4 à 6 mois), au cours de laquelle l'ensemble des marqueurs de résorption ont augmenté de 75 à 125% en vol comparé au sol, avec une perte calcique de 234 mg/jour (Smith et al., 2005a). Toutefois, ces altérations présentent des disparités au niveau des zones impactées. En effet, une augmentation de la densité minérale crânienne est observée suite aux missions de longue durée, tandis que celles du thorax ou des bras restent stable. Les pertes les plus importantes sont observées au niveau du pelvis et du fémur proximal (>1% par mois), représentant 97% de la perte totale de densité minérale osseuse corporelle, malgré des apports énergétiques et vitamine D adéquats, résultant en un risque accru de fractures (LeBlanc et al., 2000a; Vico & Hargens, 2018) (**Figure 4**).

3.1.4.Masse et composition corporelle

Depuis les premières missions à bord des navettes spatiales (4-19 jours)(Stein et al., 1999b; Wade et al., 2002), Mir (4 mois) (Smith et al., 2001; Smith et al., 1999) ou les premières missions à bord de l'ISS (4-6 mois) (Matsumoto et al., 2011; Smith et al., 2005b), une perte de masse corporelle supérieure à 5% de la masse initiale a été observée indépendamment de la durée de la mission, et ce malgré des apports énergétiques en accès suffisant (Laurens et al., 2019). Dans certains cas, cette perte pouvait atteindre jusqu'à 10%, ce qui est cliniquement significatif. Toutefois, la masse corporelle est restée stable dans certaines missions, notamment au cours du programme de navettes spatiales Space Life Science SLS-1 et SLS-2 dans les années 1990s (Stein et al., 1996) ou suites aux missions plus récentes à bord de l'ISS (Smith et al., 2012; Smith et al., 2005b). Aujourd'hui, les rapports montrent que les astronautes continuent de perdre en moyenne 2 à 5% de leur masse initiale, bien qu'une grande variabilité-interindividuelle soit reportée (Matsumoto et al., 2011; Zwart et al., 2014). Cette perte de masse corporelle serait le résultat d'un couplage altéré entre les apports et les dépenses, résultant en un déséquilibre de la balance énergétique (Laurens et al., 2019; Stein, 2001).

Plus particulièrement, les changements de composition corporelle (i.e. masse grasse et masse musculaire) constituent un véritable enjeu médical et opérationnel, notamment pour les missions futures planifiées par les différentes agences spatiales avec des durées prévues largement supérieures à celles actuellement réalisées par les astronautes (5 à 6 mois sur l'ISS). Ainsi, la régulation de la balance énergétique en milieu spatial apparaît comme un axe de recherche prioritaire des agences spatiales (Sawin et al., 2007). En effet, la limitation des stocks alimentaires liés aux contraintes de stockage et de conservation en vol impose la quantification au plus juste de la DETJ des astronautes pour optimiser les performances et la santé des astronautes, mais également optimiser les coûts induits par l'envoi de matériel dans l'espace (Jones, 2018; Laurens et al., 2019).

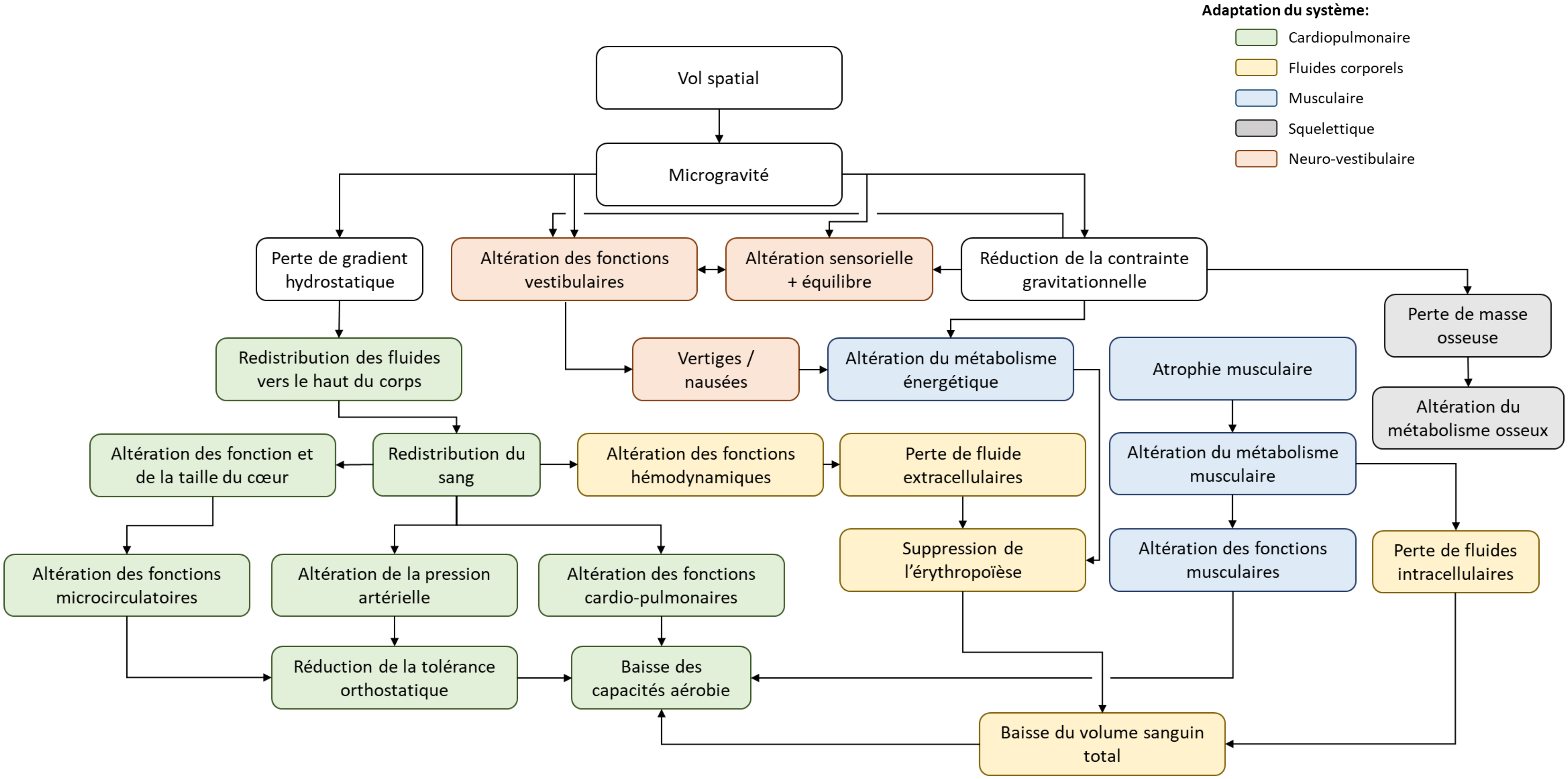


Figure 4: Représentation schématique des adaptations induite par la microgravité associée aux vols spatiaux. Adapté de Vernikos (1986).

3.2. Le maintien de la condition physique au cours des missions spatiales

3.2.1.Les modèles analogues terrestres

Si la recherche biomédicale en vol représente un réel intérêt dans la compréhension des adaptations physiologiques induites par la microgravité, ou d'autres altérations communément observées sur Terre (e.g. sarcopénie, ostéoporose, remodelage cardiaque, etc.), elle reste un modèle d'exception. Dans un contexte d'exploration extra planétaire impliquant des vols pouvant durer jusqu'à plusieurs années (contre six mois habituellement à bord de l'ISS actuellement), la compréhension des adaptations physiologiques induites par la microgravité et le développement de contremesures optimales est nécessaire. Pour ce faire, différents modèles analogues terrestres ont été mis au point par les agences spatiales telles que la suspension du membre inférieur chez l'animal, les vols paraboliques, l'immersion sèche ou encore les alitements prolongés à tête déclinée (head down tilt bedrest).

Historiquement, l'alitement était utilisé à des fins médicales afin de traiter certaines pathologies nécessitant un repos théorique. Ce n'est qu'à partir du XXème siècle où l'alitement a été pensé comme modèle analogue aux séjours prolongés en microgravité. Après avoir observé une perte de calcium osseux chez des étudiants alités durant 6 à 7 semaines, Whedon a émis un parallèle avec le milieu spatial, où les astronautes n'utilisaient plus leur membre inférieur pour supporter leur poids corporel dû à la microgravité (Deitrick et al., 1948). Les premiers modèles analogues terrestres étaient basés sur l'immersion, mais celle-ci s'avérait rapidement inconfortable pour les participants et limitaient ainsi la durée des études, conduisant les groupes de recherche à privilégier le modèle de l'alitement. Si ce dernier permet de reproduire l'hypokinésie et l'hypodynamie (baisse des mouvements corporels et de la force / puissance respectivement) observées en vol, il ne permet pas de reproduire la redistribution des fluides induite par la microgravité. En se basant sur des angles choisis arbitrairement de -15°, -10° et -5° pour reproduire le confort, l'adéquation et la magnitude des réponses induites par le vol décrites par les cosmonautes russes ; un angle décliné de -6° a été retenu comme le meilleur compromis, considéré comme le plus représentatif des sensations induites par la microgravité par les cosmonautes soviétiques (Atkov & Bednenko, 1992). Depuis plus de 30 ans, l'alitement décliné est largement utilisé et considéré comme représentatif des conditions induites par les vols spatiaux (i.e. recréé les mêmes contraintes à l'origine d'adaptations similaires), avec l'avantage de proposer un environnement ultra-contrôlé pour les équipes scientifiques (e.g. sommeil, alimentation, prélèvements, emploi du temps des participants, etc.) (Pavy-Le Traon et al., 2007). Il est ainsi possible pour les différentes agences spatiales de tester et développer les contremesures du futur qui seront à implémenter au cours des missions de la prochaine phase exploratoire de la conquête spatiale afin de préserver la santé et les performances des équipages sans compromettre le succès de la mission.

3.2.2.Les programmes de contremesure

Depuis les premières descriptions des altérations physiologiques rencontrées par les astronautes au cours des vols habités, de nombreuses contremesures ont été testées. Celles-ci ont été développées puis implémentées dans la routine des équipages afin de limiter les altérations, voire maintenir la condition physique (performances et composition corporelle) des astronautes au cours des missions de plus ou moins longue durée (i.e. de quelques jours à plusieurs mois) (Cahill & Hardiman, 2020; Convertino, 2002). Les approches nutritionnelles sont basées principalement sur des compléments alimentaires spécialisés et des formules antioxydantes pour les astronautes (Cena et al., 2003). Or, l'élaboration d'un système de nourriture spatial doit faire face à de nombreuses contraintes liées au stockage des réserves, à la stabilité des aliments, aux valeurs nutritionnelles ou encore à la variété des repas rendant sa mise en place complexe, notamment dans l'optique des missions de longue durée prévues dans le cadre de la prochaine phase de la conquête spatiale (Douglas et al., 2020).

Depuis le programme Gemini, l'exercice représente la pierre angulaire des contremesures permettant de prévenir, ou limiter le déclin des principaux systèmes physiologiques évoqués (Scott et al., 2019). Les astronautes, considérés comme des athlètes, suivent un plan d'entraînement strict composé de trois phases distinctes, à savoir une phase de préparation au sol, une phase de maintien en vol et une phase de réhabilitation à leur retour sur Terre (Hackney et al., 2015; Loehr et al., 2015). Au cours des missions actuelles à bord de l'ISS, les membres de l'équipage disposent de deux heures quotidiennes allouées à la pratique d'exercices de type aérobie et résistif (temps de préparation, hygiène, transfert des données inclus), bien qu'environ la moitié du temps alloué à l'entraînement soit dédiée à l'installation du matériel, à la préparation de la séance, au transfert de données avec les agences spatiales et à l'hygiène. D'autres stratégies complémentaires ont également été testées basées sur l'utilisation d'une gravité artificielle ou encore l'utilisation de brassards permettant de créer une pression négative sur le membre inférieur (lower body negative pressure – LBNP) pour réduire la perte de gradient hydrostatique, favoriser le retour veineux et ainsi optimiser les effets de l'exercice (Hargens et al., 2012; Harris et al., 2020).

3.2.3.La contremesure exercice

Depuis les premiers vols en orbite habités et les premières observations sur les effets de la microgravité sur les équipages, les agences spatiales se sont intéressées aux conséquences physiologiques induites par les vols spatiaux, et principalement au maintien des capacités physiologiques des équipages, avec notamment la réalisation de mesures indirectes des capacités cardiorespiratoires au cours du projet Mercury au début des années 1960. Les tests initiaux basés sur un exercice consistant à tirer sur un élastique pendant 30 secondes ont mis en évidence la réactivité du système cardiovasculaire à s'adapter aux conditions de vol grâce aux variations de fréquence cardiaque. Bien que l'exercice ait semblé bien toléré par les astronautes, des changements hémodynamiques ont été observés 24 heures après l'atterrissage, dont les conséquences à long terme pourraient s'avérer néfastes (Berry et al., 1962).

Ces observations ont conduit la NASA à considérer l'exercice comme possible contremesure à partir de 1962 (Moore et al., 2010). Le premier protocole d'exercice a été proposé pour les missions du programme Gemini (1964-1966) au cours desquelles le test de tirage avec mesure de la fréquence cardiaque était réalisé plusieurs fois au cours de la mission. Bien que les tests étaient de courtes durée avec une charge relativement faible (1 tirage/seconde à 31.8kg), les expérimentateurs ont conclu que la condition physique des astronautes n'était pas altérée après 14 jours en vol (Berry & Catterson, 1967). En plus de ces tests réalisés en vol, les résultats de l'expérimentation M003 – Inflight Exercise and Work Tolerance comprenant un test incrémental sur ergocycle en pré- et post-vol ont reporté une baisse des capacités physiques avec une augmentation de la fréquence cardiaque à l'exercice et une puissance maximale en fin d'exercice diminuée. D'autres expérimentations similaires ont été réalisées au cours du programme Apollo (1968-1972) jusqu'à la mise en place du programme Skylab en 1973, ayant permis le début des premières expérimentations sur les adaptations physiologiques en réponse à des missions de longue durée (28 à 84 jours). Ces missions ont vu la mise en place d'un test incrémental sous-maximal sur ergocycle conduit en routine par les membres de l'équipage tous les 6 jours, permettant la réalisation de mesures cardio-respiratoires (Michel et al., 1975; Rummel et al., 1976). Le programme Space Shuttle (missions Space Life Science SLS-1 et SLS-2) a permis le développement d'exercice réguliers comme contremesure au cours de la mission (9 et 14 jours). Les astronautes disposaient d'un tapis de marche non-motorisé, bien qu'aucun entraînement spécifique n'ait été prescrit. L'utilisation régulière du tapis a permis aux astronautes de maintenir leur VO_2max (consommation maximale d'oxygène) stable entre le début et la fin de la mission, tandis que ceux ne l'ayant pas utilisé ont montré une baisse de 10% de VO_2max. De plus, les astronautes ayant utilisé régulièrement le tapis au cours de la mission ont observé une augmentation moins marquée de la fréquence cardiaque à l'exercice, une puissance maximale produite à la fin d'un test incrémental sur ergocycle plus élevée et une perte de masse corporelle moins importante au retour sur Terre comparativement aux astronautes n'ayant pas utilisé le tapis (Lee et al., 1999; Siconolfi et al., 1994).

Si les contremesures pionnières étaient axées sur une protection cardiovasculaire avec des exercices de type aérobie, le développement de l'exercice en tant qu'entraînement s'est développé sur l'ISS avec la mise en place d'appareils d'entraînement en aérobie (tapis de course TVIS puis T2 et ergocycle CEVIS) et résistif (appareil multi-mouvement iRED puis ARED) (**Figure 5**) (Moore et al., 2010; Scott et al., 2019). L'amélioration des appareils au niveau de la charge de travail (vitesse du tapis, résistance de l'ergocycle, résistance de l'appareil de renforcement musculaire multi-mouvement) et l'optimisation des entraînements (i.e. volume, adaptation de la charge du travail, phases de travail adaptées au timing de la mission, etc.) (Hackney et al., 2015; Loehr et al., 2015; Petersen et al., 2016) sur des missions de longue durée (>100 jours) ont permis de limiter le déclin des performances cardiorespiratoires et musculaires, ainsi que le maintien de l'intégrité du système musculosquelettique (Comfort et al., 2021; English et al., 2020).

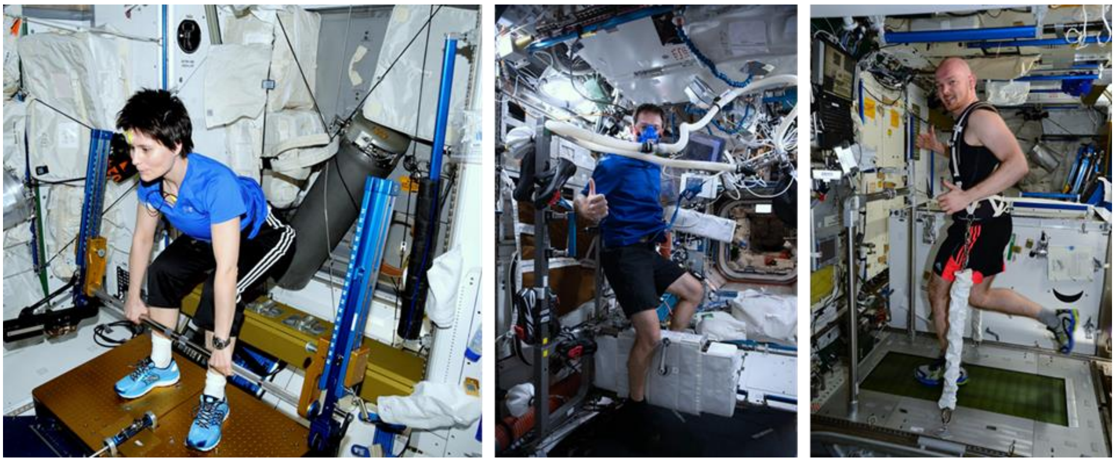


Figure 5: Appareils d'exercice utilisés à bord de la Station Spatiale Internationale.
De gauche à droite : Astronaute de l'ESA Samantha Cristoforetti utilisant l'ARED (Advanced Resistive Exercise Device – entraînement résistif), astronaute de l'ESA Thomas Pesquet utilisant le CEVIS (Cycle Ergometer with Vibration Isolation and Stabilization system – ergocycle) et astronaute de l'ESA Alexander Gerst utilisant le T2 (Treadmill with Vibration Isolation Stabilization 2nd generation) – Droits d'auteur ESA / NASA.

Messages clé

- Après le premier vol en avion motorisé en 1903 et le premier homme dans l'espace en 1961, la prochaine phase de la conquête spatiale a pour objectif à terme l'établissement d'une colonie humaine sur la Lune, puis la conquête de mars d'ici les années 2030, imposant des missions pouvant durer jusqu'à plusieurs années, contre six mois actuellement à bord de l'ISS.
- La microgravité induite par l'environnement spatial est à l'origine de nombreuses adaptations touchant l'ensemble des systèmes physiologiques (musculosquelettique, cardiovasculaire, proprioceptif, hormonal, immunitaire, etc.) pouvant menacer les performances et la santé des astronautes et par conséquent, le succès de la mission.
- L'exercice est utilisé depuis les années 1950 comme pierre angulaire des programmes de contremesure visant à prévenir les adaptations physiologiques induites par l'exposition prolongée à la microgravité.
- Plus de deux heures quotidiennes sont allouées à la pratique d'exercice en aérobie et résistif au cours des missions à bord de l'ISS, réparties sur des exercices de course à pied, cyclisme et musculation (ciblant l'ensemble des groupes musculaires).

3.3. Régulation de la balance énergétique en microgravité

L'impact de la microgravité sur les différents systèmes physiologiques a largement été décrit au cours des dernières décennies (Demontis et al., 2017; Vernikos, 1996). De plus, les données issues de microgravité réelle ou simulée suggèrent que les adaptation induites par cette dernière seraient amplifiées en situation de déficit énergétique prolongé (Bergouignan et al., 2016) (**Figure 6**). Un déficit énergétique prolongé favorisera ainsi l'atrophie musculaire, notamment due à une réduction de la synthèse protéique (Stein et al., 1999a), et par conséquent la perte de masse osseuse (Bettis et al., 2018). Les musculaires et cardiovasculaires sont également altérées en cas de déficit énergétique (Smith et al., 2002), favorisant ainsi le déconditionnement physique.

Une balance énergétique négative ne peut être que le résultat d'apports énergétiques insuffisants pour couvrir les besoins imposés par la mission. Or, l'exercice qui vise à prévenir des adaptations induites sur les systèmes cardiorespiratoire ou musculosquelettique va induire une dépense d'énergie importante, dont les apports énergétiques parfois limités ne suffiront pas à couvrir les besoins. Bien qu'elle représente un élément majeur des performances et de la santé des astronautes, la régulation de la balance énergétique en vol n'a été que très peu étudiée de façon objective.

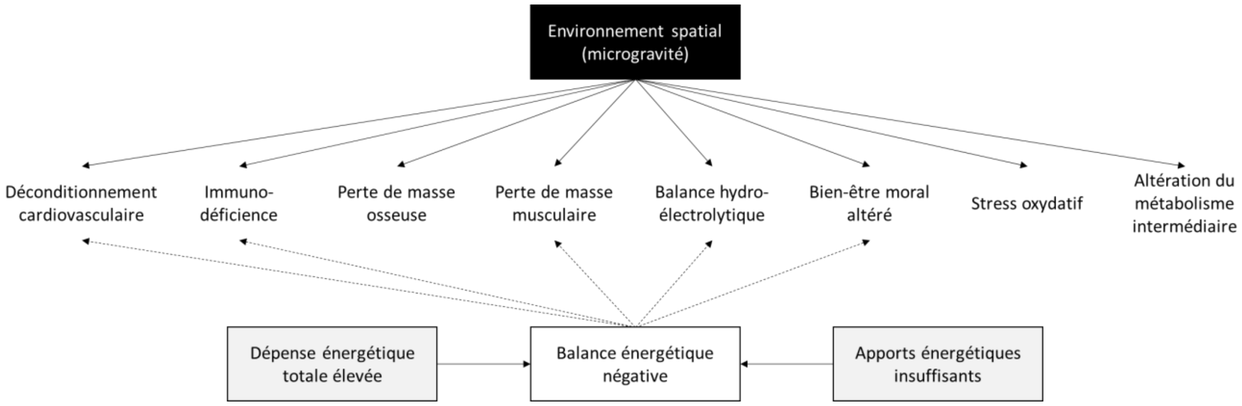


Figure 6: Adaptations induites par la microgravité et une balance énergétique observées en microgravité. Adapté de Bergouignan et al. (2016)

3.3.1.Le système de nutrition au cours des vols spatiaux

La part des apports énergétiques a largement été décrite dans la littérature en termes de quantité, ou de qualité des apports (Cahill & Hardiman, 2020; Lane & Feeback, 2002). De façon générale, les données collectées à bord de l'ISS ont montré que, malgré des apports théoriques suffisants basés sur les recommandations de l'Organisation Mondiale de la Santé (OMS), les astronautes ne consommaient environ que 80% des besoins théoriques ; une grande variabilité inter-individuelle est régulièrement reportée (Smith et al., 2005b; Zwart et al., 2014). Néanmoins, une nutrition inadéquate prolongée peut avoir des conséquences néfastes sur les différents systèmes de l'organisme. Par exemple, une baisse de la consommation de protéine amplifiera le turnover protéique à l'origine de l'atrophie musculaire, une augmentation du sodium favorisera la rétention d'eau et une balance des fluides négative, et le manque d'apport calcique amplifiera la résorption osseuse pour maintenir un taux de calcium sérique occasionnant par conséquent une perte de masse osseuse (Heer et al., 2000).

Si les réserves alimentaires basées sur les apports théoriques sont suffisantes à bord de l'ISS (et ajustés si besoin grâce aux ravitaillements cargo), une « anorexie spatiale » a été observée au cours des différentes missions et pourrait expliquer la diminution de la prise alimentaire (Varma et al., 2000). Cette dernière étant un comportement biopsychologique complexe (Blundell, 1991), l'un des premiers aspects décrit par les astronautes est le manque d'attractivité de la nourriture dont le choix limité peut conduire à une certaine monotonie, et où les conditions de stockages (e.g. lyophilisation) et l'environnement du vaisseau (e.g. CO_2 élevé, bruit, odeurs, etc.) peuvent altérer les perceptions alimentaires (goût et odorat) (Taylor et al., 2020). Des adaptations physiologiques sont également à prendre en compte, avec notamment la redistribution des fluides qui se met en place dès les premières heures en microgravité. L'augmentation des fluides dans la partie supérieure du corps est à l'origine d'une congestion nasale pouvant altérer la perception du goût et des odeurs (Olabi et al., 2002). Des altérations au niveau du système gastrointestinal ont également été mises en avant, avec une incapacité d'expulser les gaz à l'origine d'inconfort (Cena et al., 2003) ; toutefois, la mobilité intestinale ne semble pas être altérée en condition de microgravité. Enfin, les réponses hormonales à la microgravité pourraient expliquer cette altération de l'appétit, avec notamment une augmentation de la sécrétion de leptine en vol ; la leptine étant une hormone sécrétée par le tissu adipeux connue pour son rôle dans l'augmentation de la satiété et la diminution de la prise alimentaire (Stein et al., 1999c).

3.3.2.La dépense énergétique totale des astronautes

La dépense énergétique des astronautes n'a été que très peu étudiée en vol, notamment en raison des contraintes logistiques et économiques des missions spatiales. Seules trois études ont étudié la régulation de la balance énergétique au cours de missions de courte-durée en mesurant la DETJ de façon objective avec l'utilisation de l'eau doublement marquée (technique de référence pour mesurer objectivement et précisément la DETJ en conditions de vie libre) (Lane et al., 1997a; Stein et al., 1996; Stein et al., 1999b) ; deux d'entre elles ayant conclu que la régulation de la balance énergétique n'était pas optimale en condition de microgravité. Plus spécifiquement, les résultats de ces études montrent que les compensations alimentaires ne suffisent pas à équilibrer la DETJ des astronautes au cours des missions spatiales (Stein, 2001).

Au cours des 17 jours des missions Life and Microgravity Science (LMS) à bord des navettes spatiales, les quatre astronautes dépensaient en moyenne 13.9 MJ/jour (3 320 kcal/jour) résultant en un déficit énergétique de l'ordre de 5.7 MJ/jour (1 355 kcal/jour). Ce déficit énergétique s'est traduit par une perte de 2kg de masse grasse (Stein et al., 1999b). Malgré la mise en place d'une contremesure exercice visant à lutter contre la perte de masse osseuse et l'atrophie musculaire, les astronautes présentaient une balance azotée négative indiquant un mauvais ajustement entre les apports énergétiques et protéiques, et les dépenses. De façon opposée, les astronautes des missions SLS-1 et SLS-2, au cours desquelles aucun protocole d'exercice n'était prescrit, ont maintenu une balance énergétique stable, bien qu'une légère balance azotée négative ait été reportée. Toutefois, les apports protéiques étaient couverts, et les apports énergétiques spontanément diminués pour s'adapter à la réduction de la DETJ (Stein et al., 1996).

Si l'exercice apparaît comme la pierre angulaire des contremesures des missions spatiales pour maintenir, ou prévenir le déclin, de l'ensemble des systèmes physiologiques (Comfort et al., 2021; Scott et al., 2019), son coût énergétique associé ne semble pas être compensé par des apports énergétiques adéquats. Un volume élevé d'exercice serait ainsi à l'origine d'altérations de la régulation de la balance énergétique dont les conséquences peuvent s'avérer néfastes, voire critique, dans le succès des missions à long terme. En effet, bien que Stein ait proposé d'estimer les besoins énergétiques (E) des astronautes au cours des missions spatiales à partir l'équation $\mathrm{E} = 1.40\ \times \mathrm{MR} + \mathrm{DEEx}$ (MR étant le métabolisme de repos et DEEx la dépense énergétique induite par l'exercice) (Stein et al., 1999b), le coût énergétique de l'activité physique en vol (exercice + activités de la vie quotidiennes) n'a jusqu'à présent jamais été mesuré.

Chapitre 3. Mesure de la balance énergétique et ses composantes

1. Mesure des apports énergétiques

La quantification objective et précise des apports énergétiques s'avère complexe, voire fastidieuse. En effet, il est nécessaire de dissocier l'énergie ingérée via l'alimentation, de l'énergie assimilée qui sera stockée ou utilisée comme substrat énergétique (Fernández-Verdejo et al., 2019).

Pour mesurer la quantité d'énergie ingérée, les outils indirects et subjectifs sont les plus utilisés avec notamment les enquêtes alimentaires et journaux de bord remplis à la journée ou sur un rappel allant d'un à plusieurs jours de façon prospective ou rétrospective permettant d'avoir accès au type d'aliment consommé, leur quantité et leur fréquence (Thompson & Byers, 1994). Si ces outils s'avèrent efficaces pour des larges échantillons en raison de leur faible coût et facilité d'analyse, ils restent soumis à la subjectivité du sujet qui peut avoir tendance à oublier ou sous-estimer ses apports, voire influencer sa prise alimentaire habituelle (Trabulsi & Schoeller, 2001). Ainsi, leur utilisation doit être limitée si i) la prise alimentaire correspond à une variable d'intérêt principale et ii) si les sujets observent une période en vie libre entre les différents temps de mesure.

D'un point de vue physiologique, un équilibre de la balance énergétique signifie que les apports énergétiques sont égaux à la somme des dépenses énergétiques. Par conséquent, la mesure de la DETJ permet de déduire objectivement les apports énergétiques (World Health Organization, 2010). En cas de balance énergétique déséquilibrée, les changements de composition corporelle permettront d'estimer les variations de réserve énergétique puisque l'énergie ne peut être ni crée ni détruite, mais transformée (Thomas et al., 2011). Ainsi, les apports énergétiques correspondent à la somme de la DETJ et des changements de stocks énergétiques, c'est-à-dire aux changements de composition corporelle en appliquant un coefficient énergétique à chaque tissu (0.04 MJ/g – 9.5 kcal/g de masse grasse et 0.004 MJ/g – 1.1 kcal/g de masse maigre) (Ravelli & Schoeller, 2021). Mathématiquement, cela revient à utiliser l'équation suivante :

$$\mathrm{AE}_{(\mathrm{kcal/jour})} = \mathrm{DETJ}_{(\mathrm{kcal/jour})} + \frac{\left(\Delta\mathrm{MG}_{(\mathrm{kg})} \times 9500_{\mathrm{kcal/jour}}\right) + \left(\Delta\mathrm{MM}_{(\mathrm{kg})} \times 1100_{\mathrm{kcal/jour}}\right)}{\mathrm{nb\ de\ jour}}$$

Où AE= apports énergétique, DETJ= dépense énergétique totale journalière, ΔMG= changement de masse grasse sur la période de mesure, ΔMM= changement de masse maigre sur la période de mesure (MM= masse totale – MG).

A travers une revue de la littérature, Ravelli et Schoeller ont montré que le calcul des AE basé sur le concept de balance énergétique avait une exactitude de 2% et une précision de 4 à 37% en fonction des méthodes utilisées pour calculer la DETJ et mesurer les changements de composition corporelle, ainsi que la durée de la période de mesure observée (la précision augmentant avec la durée de la période de mesure). Ainsi, dans un contexte de vie libre où les apports ne sont pas contrôlés (environnement lointain ou isolé), cette méthode apparaît comme celle de référence pour estimer précisément et objectivement les apports énergétiques.

2. Mesure de la dépense énergétique et ses composantes

Les différentes études présentées dans ce manuscrit sont basées sur une méthodologie similaire détaillée dans la **figure 7**, permettant d'étudier la dépense énergétique totale et ses composantes.

2.1. La dépense énergétique totale

La méthode de l'eau doublement marquée est considérée comme la méthode de référence (« gold standard ») dans la mesure du métabolisme énergétique de façon non-invasive en condition de vie libre chez des populations variées allant de l'enfant au sénior, en passant par l'athlète de haut niveau ou la femme enceinte avec une exactitude de 2% et une précision de 2 à 10% (Bhutani et al., 2015). Cette technique, qui repose sur la mesure de production du dioxyde de carbone (CO_2) à travers l'élimination des isotopes stables non-radioactifs (^2H et ^{18}O), a été validée pour la première fois chez l'animal par Lifson et McClintock en 1955, puis chez l'Homme par Schoeller et van Santen en 1982 (Lifson et al., 1955; Schoeller, 1988; Schoeller & van Santen, 1982). Si l'utilisation de l'eau doublement marquée était limitée à ses débuts, elle s'est par la suite développée notamment grâce à la baisse des coûts des isotopes stables et à l'augmentation de la sensibilité des spectroscopes de masse à rapports isotopiques utilisés pour mesurer l'enrichissement isotopiques des différents échantillons.

La mesure de la DETJ par eau doublement marquée repose sur l'ingestion par l'individu d'un bolus d'eau enrichie en deutérium et oxygène 18 ($^2H_2{}^{18}O$). Après s'être équilibrée avec l'eau corporelle déjà présente dans les différents compartiments, l'eau marquée va progressivement être évacuée, et la concentration en isotope dans l'organisme va diminuer de 5 à 20% par jour. Tandis que le $^2H_2$ sera évacué sous forme d'H_20, le ^{18}O sera évacué sous forme d'H_2O et CO_2. Ainsi, la différence entre les deux taux d'élimination des deux isotopes donnera une production de CO_2 qui pourra être convertie en consommation d'énergie grâce aux équations classiques de calorimétrie indirecte (Racette et al., 1994; Schoeller, 1988; Weir, 1949) (**Figure 7**).

Dans la pratique, il est demandé au sujet de réaliser un premier prélèvement permettant de déterminer le rapport des abondances atomiques de deux isotopes d'un même élément ; ici $^{2}H/^{1}H$ et $^{18}O/^{16}O$ initiaux, pouvant varier selon le régime alimentaire, la localisation géographique, la saison, etc. (Bhutani et al., 2015). Après avoir ingéré la dose calculée sur sa masse corporelle, le sujet devra observer une période de calme avec un minimum d'activité physique afin de permettre aux isotopes de la dose de s'équilibrer avec ceux naturellement présents dans l'eau corporelle. Cette période est plus ou moins longue selon l'espèce étudiée ; chez l'homme l'équilibre est atteint au bout de 4 à 6 heures dans l'urine ou le plasma, et 3 à 4 heures pour la salive. Une fois cette période passée, le sujet devra fournir un échantillon permettant de mesurer l'enrichissement maximal. La mesure de l'enrichissement isotopiques peut se faire à partir des différents fluides (i.e.¸ sang, urine, salive, lait maternel) recueillis au cours de la période de mesure. Les échantillons seront prélevés plus ou moins fréquemment selon le budget et l'exactitude de la mesure souhaitée, permettant de calculer la perte d'enrichissement au cours du temps qui se fait de façon exponentielle. La période de mesure optimale est de 1 à 3 demi-vies du deutérium (^{2}H), soit 3 jours chez l'enfant ou les athlètes de haut niveau (qui auront un turnover hydrique élevé) et 2 à 3 semaines pour les sujets âgés sédentaires. Chez l'homme adulte sain, une période de 10 à 14 jours est couramment utilisée (Bhutani et al., 2015) (**Figure 7**). Les échantillons seront ensuite cryo-distillés ou filtrés afin d'obtenir l'eau la plus pure possible. Si la première est considérée comme la méthode de référence, elle requiert une certaine expertise technique et reste relativement chronophage (Chery et al., 2015).

2.2. Le métabolisme de repos

La mesure du MR renvoie historiquement aux travaux pionniers de Lavoisier et Seguin à la fin du XVIIIème siècle, qui ont décrit une augmentation de la consommation d'O_2 suite à la pratique d'activité physique ou une prise alimentaire. Ils ont observé que la combustion d'une bougie, tout comme l'activité respiratoire d'un animal, éliminaient l'oxygène de l'air, concluant que le métabolisme était un « processus de combustion interne » naturel impliquant la consommation d' « air vital » (O_2) et la libération d' « air fixe » (CO_2) (Niklas & Kutschera, 2015). C'est sur ce principe que la mesure de la consommation d'O_2 et ou de la production de CO_2 (en fonction de l'appareil utilisé) sera réalisée et à jeun (>6 heures), allongé (et éveillé), en neutralité thermique (20-25°C) et sans avoir pratiqué d'activité physique modérée à intense dans les 14h précédent la mesure, afin de ne pas stimuler les autres postes de dépense énergétique. Après avoir observé une période de repos de 10 à 20 minutes permettant au sujet d'être dans un état stable (<10% de variation dans les volumes d'O_2 inspiré et CO_2 expiré), la mesure va pouvoir débuter à l'aide d'un masque, ou canopy, voire d'une chambre calorimétrique, tout en évitant les fuites d'air (Compher et al., 2006). La mesure des volumes d'O_2 inspiré et du CO_2 expiré peut être réalisée sur une période d'au moins 20 minutes, en excluant les 5 premières et 5 dernières minutes, afin de garder 10 minutes en état stable. Les volumes de gaz consommés seront ensuite convertis en dépense énergétique grâce aux équations de Weir (Weir, 1949). Tout comme la DETJ, le MR va être déterminé par la masse du sujet avec une relation quasi-linéaire comme décrit par la Loi de Kleiber dans les années 1930, principalement par la masse métaboliquement active, c'est-à-dire la masse maigre (Kleiber, 1947; Niklas & Kutschera, 2015). Plus précisément, le MR serait déterminé à 63% par la masse maigre, 6% par la masse grasse et 2% par l'âge (Johnstone et al., 2005). La composition de la masse maigre est également à prendre en compte, avec un coefficient calorique appliqué pour les différents tissus (Elia, 1992; Sparti et al., 1997; Wang et al., 2010) (**Tableau 1**).

Tableau 1: Contribution des différents tissus dans la détermination du métabolisme de repos.

	Masse (kg)	**Coefficient d'Elia (MJ/kg/jour [kcal/kg/jour])**	**% MR mesuré**
Foie	1.39	0.84 [200]	17.65
Cerveau	1.33	1.00 [240]	20.27
Cœur	0.31	1.84 [440]	8.66
Reins	0.29	1.84 [440]	8.10
Muscle squelettique	26.3	0.05 [13]	21.71
Tissu adipeux	19.4	0.02 [4.5]	5.54
Masse résiduelle	24.7	0.05 [12]	18.82

Tableau basé sur les coefficients d'Elia décrit par Wang et al. (2010). Les masses des différents tissus ont été mesurées sur un échantillon de 131 individus (67 hommes, 64 femmes, âge= 41.8 (SD 14.8) ans, IMC= 24.2 (2.9) kg/m²) avec un métabolisme de repos (MR) moyen mesuré par colorimétrie indirecte de 6.9 MJ/jour (1575 kcal/jour).

Si la mesure du MR requiert l'utilisation d'appareils spécifiques et les contraintes associées (coût, logistique, expertise, durée d'acquisition de la mesure, etc.), des méthodes alternatives basées sur des équations prédictives ont été développées, avec l'avantage de pouvoir être appliquées sur de larges cohortes. Si plus de 248 équations ont été développées permettant d'estimer le MR sur des rangs divers d'âge, de genre, d'ethnie ou de paramètres anthropométriques, les plus répandues étant celles de Harris et Benedict en 1918 (Harris & Benedict, 1918), Schofield en 1985 (Schofield, 1985) et l'OMS en 1985 (FAO/WHO/UNU, 1985), Owen en 1986-87 (Owen et al., 1987; Owen et al., 1986), Mifflin et St Jeor en 1990 (Mifflin et al., 1990), ou encore celles de Sabounchi en 2014 basées sur des coefficients de méta-régression permettant d'adapter l'équation en fonction des caractéristiques individus (Sabounchi et al., 2013). Si ces équations permettent d'estimer un MR plus ou moins proche de celui mesuré par calorimétrie indirecte, les équations de Harris et Benedict et de l'OMS ont montré une précision de 76.7% et 66.7% (Flack et al., 2016), tandis que celles de Mifflin et St Jeor et Owen ont montré une précision respective de 82% et 73% chez des individus normo-pondérés (Frankenfield et al., 2005). Bien que cette précision soit valable à l'échelle d'un groupe, elle diminue à l'échelle individuelle, notamment lorsque la masse maigre augmente, probablement due à la contribution proportionnelle plus faible des organes internes au MR.

2.3. La thermogénèse post-prandiale

Comme observé par Lavoisier, la consommation d'O_2 va également augmenter après une prise alimentaire, témoignant une augmentation de la dépense énergétique. Sur le même principe que la mesure du MR décrite précédemment, la consommation d'O_2 et la production et CO_2 vont être mesurées par calorimétrie indirecte, cette fois-ci après un repas, puis être convertie en dépense énergétique (Weir, 1949). La thermogénèse post-prandiale (TPP) est ainsi définie comme l'augmentation de la dépense énergétique par rapport au niveau basal à jeun divisée par le contenu énergétique de l'alimentation ingérée (Egger et al., 2001; Westerterp, 2004). Bien que la TPP peut être mesurée par calorimétrie indirecte suivant un repas standardisé, la dépense énergétique induite peut varier selon la valeur de base choisie, la composition du repas et la durée de la période de la mesure. En effet, l'augmentation de la dépense énergétique post-prandiale va durer au-delà de six heures après le dernier repas (jusqu'à 10 heure pour le processus complet). L'utilisation d'une mesure sur 24 heures en chambre calorimétrique permet de s'affranchir de certaines de ces limites en contrôlant un maximum de paramètres (Westerterp et al., 1999). De façon plus générale, la TPP est estimée à 10% de la DETJ (**Figure 7**).

2.4. La dépense énergétique induite par l'activité physique

La dépense énergétique induite par l'activité physique (DEAP) représente la composante la plus variable de la DETJ. Si elle peut être simplement calculée à partir de l'équation $\mathrm{DEAP} = \mathrm{DETJ} - \mathrm{MR} - \mathrm{TPP}$ (ou $\mathrm{DEAP} = 0.9 \times \mathrm{DETJ} - \mathrm{MR}$; le coût de la thermogénèse post-prandiale étant estimé à 10% de la DETJ), il est également possible d'approcher la dépense liée aux différentes activités de façon plus précise à travers l'utilisation de différents proxys (**Figure 7**).

2.4.1.La méthode « heart flex »

La relation quasi-linéaire entre la fréquence cardiaque (FC) et la consommation d'O_2 (VO_2) a été établie dès 1914 par Murlin et Greer, puis plus précisément par Hendersen et Prince en décrivant une pente plus raide au cours des activités d'intensité modérée à intense, comparativement aux activités d'intensité légère ou un état de repos (Henderson & Prince, 1914; Murlin & Greer, 1914). C'est sur la base de ces observations que la relation entre FC et VO_2 a été établie par Booyens et Hervey en 1960, menant au développement de la méthode « Heart Flex » à la fin des années 1980, présentant un risque d'erreur de 15 à 20% dans l'estimation de la dépense énergétique comparativement à celle mesurée en chambre calorimétrique à travers des tests sur ergocycle à différentes intensités au niveau individuel, contre 2 à 3% à l'échelle du groupe (Booyens & Hervey, 1960; Spurr et al., 1988). La méthode « Heart Flex » permet d'estimer la dépense énergétique des activités lorsque celles-ci induisent une FC supérieure à celle de repos (« flex point »), tandis que pour les activités en dessous du « flex point » la dépense énergétique sera estimée à partir de la FC moyenne mesurée sur les 3 postures de repos (assis, allongé et debout). En compilant des données mesurées sur 101 individus, Leonard a observé une forte association entre dépense énergétique estimée par la méthode « Heart Flex » et celle mesurée par les méthodes de référence (i.e. eau doublement marquée et calorimétrie indirecte) ($r=0.89$; $P<0.001$; pente = 0.95 [SD 0.05]) ; 70% des sujets ayant une dépense énergétique estimée correspondant à plus ou moins 10% de la dépense énergétique mesurée (Leonard, 2003).

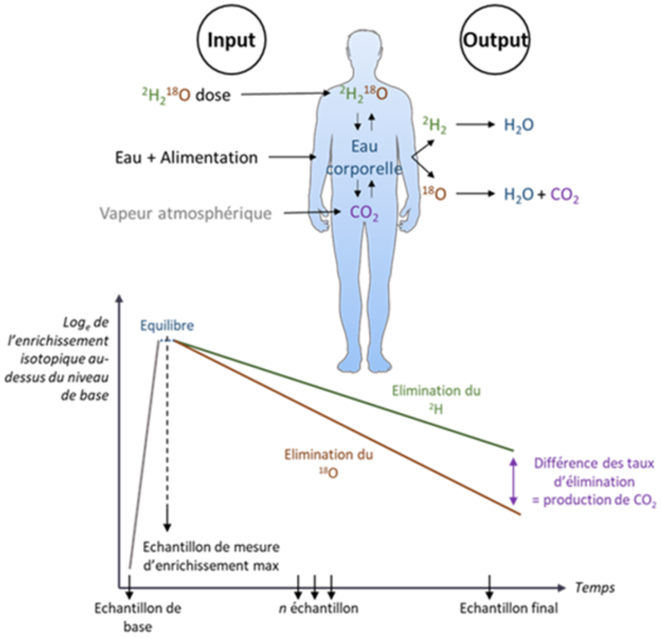
2.4.2.L'accélérométrie

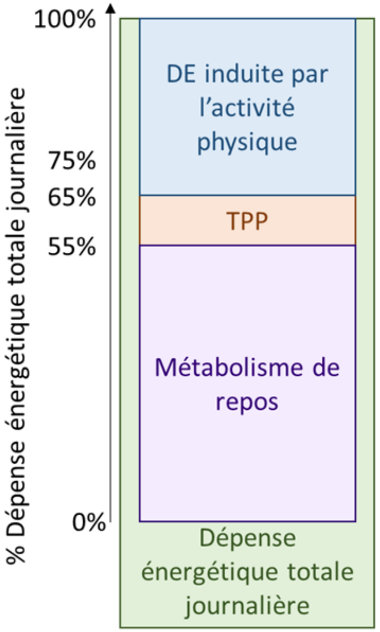
Plus récemment, le développement de l'accélérométrie a permis d'identifier des comportements, ainsi que la dépense énergétique associée à travers la mesure des accélérations dans les 3 dimensions de l'espace (i.e. antéro-postérieur, médio-latéral et vertical). Les premières analyses du genre étaient basées sur une relation considérée comme linéaire entre les accélérations et la dépense énergétique mesurée par calorimétrie indirecte sur un tapis de course à 3 vitesses différentes à la fin des années 1990 (Freedson et al., 1998). Par la suite, Schwartz et al. ont développé une analyse similaire, basée ce coup-ci sur un ensemble d'activités de la vie quotidienne (ménage, jardinage, entretien physique, entraînement sportif, etc.) (Swartz et al., 2000). Or, ces analyses ne prenaient en compte que la composante verticale de l'accélération. Afin de prendre en compte les 3 dimensions du mouvement, mais également la relation en fait non-linéaire entre accélération et dépense énergétique, de nouvelles équations ont été développées permettant d'estimer de façon plus précise la dépense énergétique associée aux différents mouvements et ainsi, mieux caractériser la DEAP (Crouter et al., 2006a; Crouter et al., 2006b). Ainsi, le développement de multi capteurs associant les accélérations mais également des paramètres physiologiques tels que la fréquence cardiaque, la température cutanée ou le flux galvanique, ainsi que le développement des algorithmes de reconnaissance permettent une analyse de plus en plus fine des patterns d'activité physique et leur impact énergétique (Andre et al., 2006; Bastian et al., 2015; Brage et al., 2005; Garnotel et al., 2018; Villars et al., 2012).

Dépense énergétique totale journalière (DETJ)

Eau doublement marquée (EDM)
Production de CO_2 sur 7 à 14 jours

- Ingestion de l'eau marquée (${}^2H_2{}^{18}O$)
- ${}^2H$ éliminé sous forme d'eau
- ${}^2H_2{}^{18}O$ éliminé sous forme d'eau + CO_2 (du à l'anhydrase carbonique)
- La différence d'élimination entre ${}^2H$ et ${}^{18}O$ correspond à la production de CO_2
- La production de CO_2 est convertie en énergie grâce aux équations de calorimétrie indirecte





Dépense énergétique liée à l'activité physique (DEAP)

Déterminée par calcul

- DEAP = DETJ – MR – TPP
  Ou
- DEAP = 0,9 * DETJ – RMR

Activité physique quotidienne et pattern d'activité physique

Déterminés par accélérométrie

- Mesure des accélérations corporelles et de la posture
- Ajout de multi-capteurs pour plus de précision (fréquence cardiaque, température cutanée, etc.)

Thermogénèse post-prandiale (TPP)

Calorimétrie indirecte: mesure de la consommation d' O_2

- Energie dépensée au cours des 5 heures suivant la prise alimentaire (EE>MR)
- Exprimée en pourcentage de la DETJ sur 24 heures
- Souvent estimé à 10% de la DETJ (0,9 * DETJ)

Métabolisme de repos (MR)

Calorimétrie indirecte: mesure de la consommation d' O_2 et production de CO_2

- Mesuré pendant 30-45 minutes à jeun, en état stable, éveillé et en thermoneutralité

Figure 7: Représentation schématique des différentes composantes de la dépense énergétique totale journalière et ses composantes.
DE= dépense énergétique ; DETJ= dépense énergétique totale journalière ; TPP= thermogenèse post-prandiale ; MR= métabolisme de repos.

3. Mesure de la composition corporelle

La composition corporelle peut être étudiée au niveau de l'atome, de la molécule, de la cellule, des tissus ou encore du corps entier à partir de modèles composés de 2 à 4 compartiments (**Figure 8**) (Wang et al., 1992). Plus le modèle a de compartiments, plus l'estimation de la composition corporelle sera précise. Cela permet ainsi de mieux comprendre les effets d'un déséquilibre sur la composition corporelle et par extension, ses effets sur les performances ou la santé (e.g. atrophie musculaire, prisse de masse grasse viscérale, ostéoporose). Or, le nombre de compartiment étudié dépendra de la méthodologie utilisée.

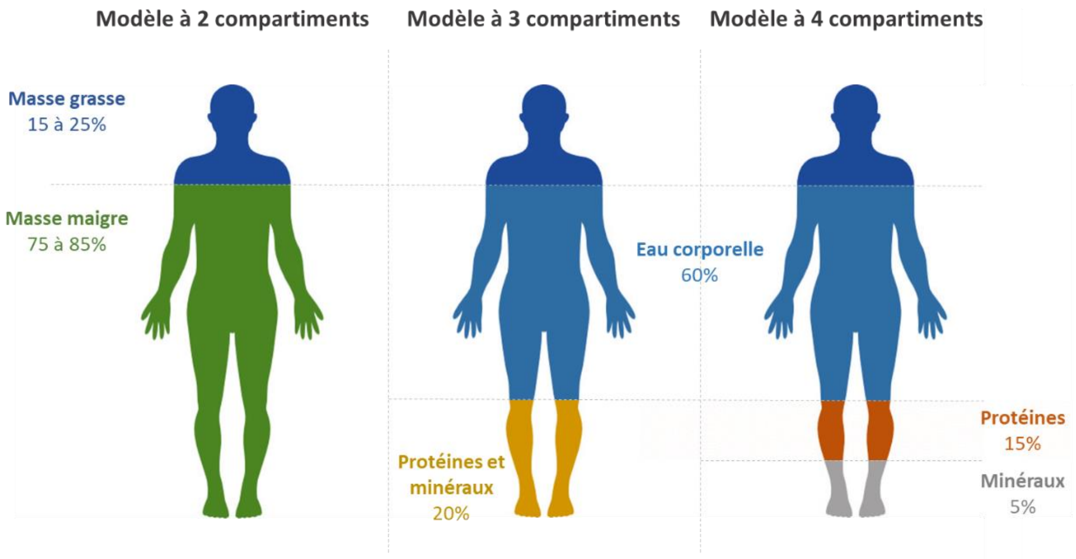


Figure 8: Représentation schématique des différents compartiments de la composition corporelle.

3.1. La dilution isotopique

Les deux compartiments peuvent être estimés par dilution isotopique, l'utilisation des isotopes de l'oxygène ($H_2{}^{18}O$) étant plus précise que celle du deutérium (^2H_2O) seul (Schoeller et al., 1980). Cette méthode repose sur l'ingestion d'un bolus d'eau marquée comme décrit précédemment. Une fois l'équilibre atteint (plus ou moins long selon la nature de l'échantillon), il sera possible de mesurer l'enrichissement isotopique de l'échantillon. En se basant sur le principe de dilution $\mathrm{n1/V1 = n2/V2}$ (n1 étant le nombre de moles de traceur dans la dose et V1 le volume de la dose d'eau ; n2 et V2 étant le nombre de moles de traceur et le volume d'eau dans le corps), il est possible de déterminer le volume d'eau corporelle totale (ECT) avec l'équation $\mathrm{V2 = n2 \times V1/n1}$. La masse maigre étant composée à ≈73% d'eau ($\mathrm{masse\ maigre = 0.73 \times ECT}$), il est possible de déduire la masse grasse en soustrayant la masse maigre à la masse totale (Pace & Rathbun, 1945; Schoeller et al., 1980; Wang et al., 1999).

3.2. La bio-impédancemétrie

La bio-impédancemétrie repose également sur une mesure de l'ECT, en se basant sur le principe que le volume d'un conducteur (l'ECT étant hautement conductrice) est proportionnel à la longueur du conducteur et inversement proportionnel à sa résistance électrique (Ward, 2019). Contrairement à la dilution isotopique dont le coût et l'expertise technique demeurent élevés et donc peu accessible, la bio-impédancemétrie est un outil abordable dont la popularité est croissante depuis les années 1985. Toutefois, la variété des types d'analyses (i.e. fréquence, région d'analyse et méthodes d'analyse des données) impose aux investigateurs une certaine prudence dans le choix des appareils et l'interprétation des données.

3.3. L'absorptiométrie biphotonique à rayon X

Pour avoir accès aux autres compartiments constituant la masse maigre, il est nécessaire de recourir à l'imagerie médicale. A ce titre, l'utilisation de l'absorptiométrie biphotonique à rayon X (DEXA pour « Dual Energy X-ray Absorptiometry ») est considérée comme la technique de référence permettant de dissocier les tissus mous (masse grasse et non-grasse) et les os (Kohrt, 1998). D'un point de vue technique, le rayon X émis par l'appareil sera atténué à la fois par les tissus mous et l'os en traversant le corps. Un second rayon sera émis avec un une énergie différente. Le coefficient d'atténuation variant entre les tissus et l'énergie des rayons, il est possible de faire la différence d'absorption entre les deux rayons pour dissocier les tissus mous des os (Kelly et al., 1998). Un traitement informatique permet ensuite de dissocier les différents tissus basés sur leurs coefficients d'atténuation au niveau du corps entier ou des différents segments. La DEXA apparaît comme une méthode robuste et fiable validée sur une large population aux caractéristiques anthropométriques variées, avec peu de variation au cours du temps et non impactée par l'hydratation de l'individu (Shepherd et al., 2017).

Problématique et Hypothèses

En raison de ses impacts multiples sur la santé et les performances, le maintien de la balance énergétique apparaît comme une priorité absolue dans le succès des différentes missions, à visée exploratoire ou scientifique. Or, les conditions extrêmes auxquelles peuvent faire face les individus peuvent mettre en péril cet équilibre en raison de dépense énergétiques élevées induites par la pratique d'exercice codifié, ou d'activités de la vie quotidienne, associées à des apports énergétiques limités voire insuffisants. Toutefois, le succès des conquêtes historiques antérieures a montré que l'Homme pouvait s'adapter dans une certaine mesure à ces différents environnements, suggérant l'hypothèse d'une régulation homéostasique de la balance énergétique basée sur des compensations physiologiques et/ou comportementales (Drenowatz, 2015; King et al., 2007). Une forte variabilité inter-individuelle a toutefois été reportée, limitant la généralisation de ces observations. L'une des principales contraintes des milieux extrêmes reste la quantité d'énergie à apporter pour couvrir les besoins élevés. Ainsi, il apparaît nécessaire d'estimer au plus juste les besoins énergétiques des individus selon les contraintes du milieu pour optimiser le coût, le poids mais également le stockage des rations si aucun ravitaillement n'est possible. De l'autre côté de la balance énergétique, la compréhension des mécanismes de régulation de la dépense énergétique totale et ses composantes jouera un rôle clé dans l'évolution de la composition corporelle, dans une optique de performance (tâches liées à des missions spécifiques, déplacement de charge, fonction musculaire, etc.) et de santé.

L'objectif principal de ce travail de thèse est d'estimer les besoins énergétiques des missions en environnement extrême requérant des niveaux d'activité physique contrastés, et leurs effets sur la régulation de la masse et la composition corporelle.

L'hypothèse principale est que l'activité physique, induite par l'exercice ou les activités spontanées, est le principal déterminant de la DETJ. Toutefois, les apports énergétiques ne peuvent pas compenser l'augmentation importante de la DETJ, résultant en une balance énergétique négative. Une balance énergétique déséquilibrée est à l'origine de modifications de la composition corporelle sans nécessairement impacter la masse totale mais dont l'impact sur les performances et/ou la santé peut s'avérer néfaste. Une diminution de l'activité physique peut s'accompagner d'une perte de masse maigre due à l'inutilisation de la masse musculaire au bénéfice d'une prise de masse grasse (stockage d'énergie), tandis qu'une augmentation de l'activité physique peut être à l'origine d'une perte de masse grasse afin de fournir l'énergie nécessaire au maintien des performances et de la masse maigre.

Ce travail de thèse s'articule autour de trois études dont les modèles permettent d'étudier l'impact de niveaux contrastés d'activité physique sur la régulation de la balance énergétique, à savoir les études ENERGY, MNX et POWER (**Figure 9**).

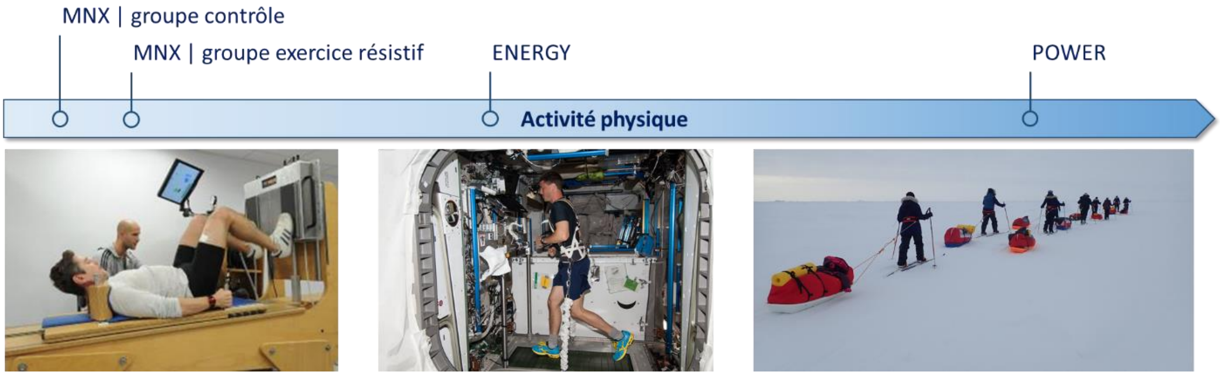


Figure 9: Représentation schématique des différents modèles d'activité physique.
MNX= étude basée sur un modèle d'alitement prolongé de 21 jours avec ou sans contre mesure exercice résistif + vibration (détaillée au Chapitre 4) ; ENERGY= étude réalisée sur des astronaute après plus de 3 mois à bord de la Station Spatiale Internationale réalisant la contremesure exercice standard (détaillée au Chapitre 5) ; POWER= étude réalisée sur des femmes non-athlète ayant traversé le Pôle Nord à ski en autonomie totale en 8 jours (détaillée au Chapitre 6).
Crédits: MEDES, NASA, The Women's Euro-Arabian North Pole Expedition.

Bien que l'exercice soit considéré comme la pierre angulaire des programmes de contremesure par les agences spatiales, les données collectées au cours des différentes missions montrent une relation entre le volume d'activité physique et la perte de masse au cours de la mission, indépendamment de la durée de la mission. A l'inverse, la quantité d'énergie ingérée n'est pas associée à la perte de masse en vol suggérant un rôle majeur de la DETJ dans la régulation de la balance énergétique en vol (Laurens et al., 2019) (**Figure 10**).

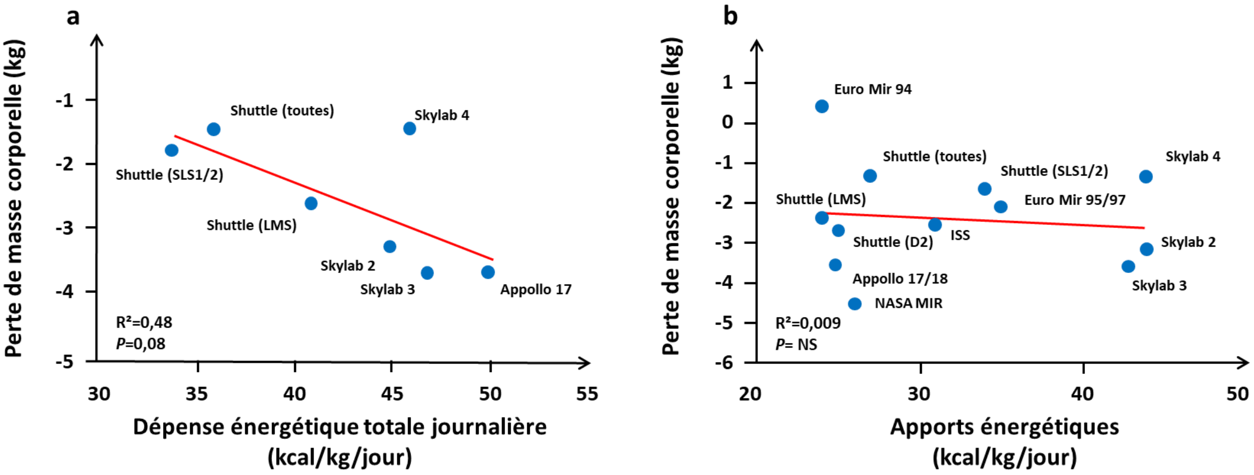


Figure 10: Relation entre la perte de masse corporelle et la dépense énergétique totale (a) et les apports énergétiques (b). Adapté de Laurens et al. (2019).

Toutefois, les rares études ayant étudié l'impact de la régulation de la balance énergétique en vol n'ont étudié que l'effet de l'exercice structuré sur des missions de courte durée, en occultant les autres composantes de l'activité physique à savoir toutes les activités spontanées de la vie quotidienne, liées ou non aux tâches de la mission. Or, l'estimation au plus juste des besoins énergétiques au cours des missions de longue durée revêt un enjeu médical et opérationnel majeur dans le succès des expéditions prévues dans la prochaine phase de la conquête spatiale. Si une altération de la masse et de la composition corporelles sont tolérables sur des courtes périodes, son impact sur le long terme va avoir des conséquences délétères. L'étude exploratoire ENERGY avait pour but d'estimer les besoins énergétiques des astronautes à bord de l'ISS en prenant spécifiquement en compte l'impact de l'activité physique (contremesure exercice permettant de prévenir des adaptations induites par la microgravité + activité spontanée quotidienne) ainsi que les changements de composition corporelle après plus de trois mois en vol. Les données ont été collectées chez onze astronautes masculins sélectionnés par les agences spatiales américaine, canadienne, européenne et japonaise. L'hypothèse était que l'activité physique en vol, principalement déterminée par l'entraînement, serait le principal déterminant des changements de masse et de composition corporelle.

Le programme d'entraînement des astronautes en vol est composé de sessions quotidiennes d'aérobie et de résistif. Afin de tester et optimiser les modalités d'entraînement, les agences spatiales utilisent des modèles analogues terrestres permettant de simuler la microgravité, telles que l'alitement prolongé en position déclinée. Des données issues d'alitement prolongé ont montré qu'un entraînement combinant des exercices en aérobie et résistif (comme actuellement prescrit à bord de l'ISS) permettait de prévenir l'atrophie musculaire habituellement observée suite à l'inactivité induite par ce modèle. Toutefois, les apports énergétiques estimés pour couvrir les besoins théoriques n'ont pas suffi à compenser la dépense énergétique induite par l'entraînement, résultant en une balance énergétique négative et une perte de masse grasse. En réponse à ces observations, les agences spatiales se sont intéressées aux effets d'un entraînement résistif (couplé à la vibration pour optimiser les bénéfices de la contraction musculaire). Toutefois, l'effet de ce type d'entraînement sur la régulation de la balance énergétique reste méconnu. L'étude MNX était un cross over permettant de comparer les effets de deux modalités de contremesure (exercice résistif + vibration, la vibration étant utilisée pour amplifier les bénéfices de la contraction musculaire sur le maintien de la masse musculaire) au cours d'un alitement prolongé (modèle terrestre analogue permettant de simuler les effets de la microgravité) de 21 jours à un alitement strict sur la régulation de la balance énergétique et la régulation de la composition corporelle chez 12 hommes adultes sains normo-pondérés. L'hypothèse était que la diminution de la DETJ due à l'inactivité physique ne serait pas différente entre les deux traitements, et n'impacterait pas la prise alimentaire permettant une balance énergétique stable. L'exercice permettrait par ailleurs de prévenir l'atrophie musculaire habituellement observée au cours des alitements prolongés sans contremesure.

A l'extrémité opposée du spectre d'activité physique, les expéditions en autonomie en condition extrême vont être à l'origine d'une DETJ importante face à des apports énergétiques en condition parfois limitée. A l'inverse des modèles précédents, l'environnement polaire va induire une augmentation conséquente de la DEAP induite par une augmentation de l'exercice mais également des activités spontanées. Or, le coût de l'acclimatation au froid pour des individus non-habitués n'est jamais considéré dans l'estimation des besoins théoriques pour une telle expédition, favorisant l'apparition d'un déséquilibre de la balance énergétique. Il est ainsi nécessaire de quantifier au plus juste en situation réelle les besoins énergétiques d'une expédition en autonomie totale en environnement polaire. Si la très grande majorité des études se sont focalisées sur des populations masculines, les femmes demeurent sous-représentées. L'étude POWER, incluant onze femmes non-athlètes participant à l'expédition Women Euro-Arabian North Pole Expedition 2018 avait pour but de mesurer pour la première fois les besoins énergétiques des femmes et comprendre les adaptations des différentes composantes de la balance énergétique au cours d'une expédition polaire visant à rejoindre le Pôle Nord en ski en autonomie totale. L'hypothèse était que l'activité physique élevée en condition extrême induirait une dépense supérieure aux apports énergétique et donc une balance énergétique négative, se traduisant par une perte de masse corporelle majoritairement due à une perte de masse grasse.

Modèles d’étude et méthodes

1. Contexte en enjeux des modèles

1.1. L'étude ENERGY

L'étude ENERGY (Astronaut's Energy Requirements for Long-Term Space Flight) a été sélectionnée par les différentes agences spatiales présentes à bord de l'ISS (américaine – NASA, européenne – ESA, canadienne – CSA / ASC et japonaise – JAXA) pour déterminer les besoins énergétiques des astronautes au cours des missions actuelles à bord de l'ISS en mesurant l'activité physique spontanée (par accéléromètre) et l'exercice (journaux de bords fournis par la NASA), ainsi que les changements de composition corporelle induits. Entre 2011 et 2017, onze astronautes issus des quatre agences spatiales ont réalisé deux sessions de mesure d'une semaine. Une première session a été conduite sur Terre l'année précédant le vol afin d'avoir les valeurs de référence de masse et composition corporelles (mesurées par dilution isotopique). La DETJ sur Terre a été mesurée par eau doublement marquée et le RMR par calorimétrie indirecte, permettant de déduire la PAEE. Les astronautes étaient également équipés de capteurs multisensoriels (accéléromètre 2D, flux galvanique, etc.). Après un minimum de trois mois à bord de l'ISS, la même session de mesure sur une semaine a été réalisée afin d'étudier les effets d'une mission de longue durée sur la régulation de la balance énergétique (**Tableau 2**). En plus des techniques citées précédemment, les agences spatiales disposaient des journaux d'activité des astronautes permettant d'avoir accès au contenu des séances d'entraînement, à savoir le temps passé sur chaque appareil et l'intensité (puissance, vitesse ou charge pour le CEVIS, T2 et ARED, respectivement).

1.2. L'étude MNX

L'étude MNX (Medium duration Nutrition and vibration eXercise) est un exemple de protocole d'alitement prolongé réalisé par l'agence spatiale européennes (European Space Agency – ESA) et le Centre National d'Etudes Scientifiques (CNES) à l'institut français de médecine spatiale et physiologie (MEDES, Toulouse, France) entre 2012 et 2013. Ce protocole est une étude randomisée cross-over où 12 individus (hommes, adultes) ont réalisé trois sessions de 21 jours d'alitement qui consistaient en une session contrôle avec un alitement strict à une session d'alitement avec un entraînement résistif avec vibration (RVE). Une troisième contremesure était proposée, à savoir une session d'alitement avec un entraînement résistif avec vibration et contremesure nutritionnelle à base de whey protéine et bicarbonate, mais elle n'a pas été incluse dans ces analyses. L'objectif général de l'étude était d'étudier l'effet des différentes contremesures sur le maintien de la masse musculaire, comparativement à un alitement prolongé strict au cours duquel une atrophie musculaire est couramment observée. L'objectif spécifique de l'étude présentée dans ce travail de thèse était de quantifier l'impact de la contremesure RVE sur la DETJ totale, et par extension sur la régulation de la balance énergétique.

La composition corporelle a été mesurée pendant la période ambulatoire par DEXA (BDC – baseline data collection) et les jours 1, 10 et 20 de l'alitement (HDT – head down tilt bedrest). La DETJ a été mesurée pendant la période BDC, puis de HDT1 à HDT9 et HDT10 à HDT21 par eau doublement marquée. Le RMR a été mesuré en BDC, puis tous les cinq jours. Les apports énergétiques étaient ajustés régulièrement de façon à maintenir la masse grasse stable (**Tableau 2**).

1.3. L'étude POWER

L'étude POWER (Physiological adaptatiOns in WomEn during a NoRth Pole expedition) a été réalisée dans le cadre de la Women Euro-Arabian North Pole Expedition 2018 qui consistait à rejoindre le Pôle Nord en autonomie totale en ski, c'est-à-dire en tractant individuellement leurs traineaux comprenant vêtements, tentes et rations alimentaires. Douze femmes issues de différents pays occidentaux et orientaux (Royaume-Uni, Arabie Saoudite, Suède, Koweït, Slovénie, Oman, France, Qatar, Russie et Chypre) ont été sélectionnées sur plus de 1 000 candidatures afin de créer un groupe de femmes représentatif, avec des âges, expériences, professions, cultures, ou familles diverses. La DETJ a été mesurée au cours de l'expédition par eau doublement marquée, et l'activité physique quantifiée par accélérométrie 3D. La composition corporelle a été estimée par bio-impédancemétrie et le RMR mesuré par calorimétrie indirecte avant et après l'expédition (**Tableau 2**).

2. Synthèse des méthodes utilisées

Tableau 2: Synthèse des méthodes utilisées et des considérations techniques spécifiques au modèle d'étude.

ENERGY	MNX	POWER
Dépense énergétique totale		
Le recyclage des urines sous forme d'eau entraîne un enrichissement isotopique progressif de l'eau de la station au cours du temps. Les astronautes participants à l'étude ENERGY buvaient dans un réservoir isolé le temps de la mesure par eau doublement marquée. Quatre astronautes contrôles ont suivi le même protocole sans ingérer d'eau doublement marquée et l'eau de la station était analysée à chaque période afin de vérifier la stabilité de l'enrichissement isotopique au cours des sessions (en 2011, 2014, 2016 et 2017). Les astronautes étaient également "sur dosé" à bord de l'ISS pour minimiser l'impact des changements d'enrichissement isotopique de l'eau de la station. Dose sur Terre : 3.00 g/kg d'eau corporelle totale (ECT) de $^{2}H_{2}{}^{18}O$ composée d'un mix de 0.30 g/kg ECT de $H_{2}{}^{18}O$ enrichi à 10% et 0.15 g/kg ECT de $^{2}H_{2}O$ enrichi à 99% (mesure de la DETJ sur 7 jours) Dose à bord de l'ISS : dose unique de $^{2}H_{2}{}^{18}O$ composée d'un mix de 105.20 g de $H_{2}{}^{18}O$ enrichi à 10% et 97% et 16.70 g de $^{2}H_{2}O$ enrichi à 99% (contraintes liées au vol : dose similaire pour tous les sujets et seringues de 60 mL maximum autorisées pour ingérer l'eau) (mesure de la DETJ sur 7 jours)	La DETJ a été mesurée en période ambulatoire et en alitement. L'alitement de 21 jours impose de réenrichir les sujets (dose à HDT1 et HDT10). L'enrichissement résiduel de la période précédente (supérieur à l'enrichissement naturel de base de l'individu) impose de diminuer la dose pour éviter les enrichissements trop importants. Dose à BDC-7 : 2.00 g/kg ECT de $^{2}H_{2}{}^{18}O$ composée d'un mix de 0.20 kg/kg ECT $H_{2}{}^{18}O$ enrichi à 10% et 0.15 g/kg ECT de $^{2}H_{2}O$ enrichi à 99% (mesure de la DETJ sur 7 jours) Dose à HDT1 : 1.60 g/kg ECT de $^{2}H_{2}{}^{18}O$ composée d'un mix de 0.16 kg/kg ECT $H_{2}{}^{18}O$ enrichi à 10% et 0.12 g/kg ECT de $^{2}H_{2}O$ enrichi à 99% (mesure de la DETJ sur 9 jours) Dose à HDT10 : 1.30 g/kg ECT de $^{2}H_{2}{}^{18}O$ composée d'un mix de 0.13 kg/kg ECT H2180O enrichi à 10% et 0.12 g/kg ECT de $^{2}H_{2}O$ enrichi à 99% (mesure de la DETJ sur 10 jours)	Le déplacement sur la banquise suggère un possible changement de l'enrichissement isotopique naturel de la glace (transformée en eau puis bue par les participantes). Des échantillons de glace ont été collectés chaque jour pour mesurer son enrichissement naturel, et une participante contrôle a suivi le même protocole sans ingérer d'eau doublement marquée permettant de vérifier et corriger pour les éventuels changements d'enrichissement isotopique naturel de la glace. Pour prendre ne compte renouvellement hydrique important induit par l'activité physique élevée au cours de l'expédition, les participantes ont reçu une dose élevée d'eau. Dose : 2.68 g/kg ECT de $^{2}H_{2}{}^{18}O$ composée d'un mix de 0.33 g/kg $H_{2}{}^{18}O$ enrichi à 13.40% et 0.22 g/kg ECT de $^{2}H_{2}O$ enrichi à 98.87% (mesure de la DETJ sur 10 jours)
Métabolisme de repos		
Le Pulmonary Function System (PFS) (Danish Aerospace Compagny, Odense, Danemark) est conçu pour mesurer la VO_2 et la VCO_2 bord de l'ISS (Clemensen et al., 1994; Moore et al., 2014).	Le Deltatrac (Datex, Madison, WI, USA) est utilisé en condition clinique pour la VO_2 et la VCO_2 chez les patients alités (Tissot et al., 1995).	Le Fitmate (Fitmate, COSMED, Rome, Italy) est utilisé pour mesurer la VO_2 seulement. L'avantage de cet appareil est d'être portable (20x40cm) et de fonctionner sur batterie, permettant une utilisation dans n'importe quel endroit (Nieman et al., 2006).
Activité physique		

Le SenseWear Pro (Body media Inc®, Pittsburgh, PA Etats-Unis) est un capteur d'activité multisensoriel placé au niveau du triceps incluant un accéléromètre 2D (Andre et al., 2006). La mesure en vol a imposé de redéfinir les activités détectées par l'appareil à partir de l'amplitude moyenne des déviations (mean amplitude deviation – MAD (Vähä-Ypyä et al., 2015a; Vähä-Ypyä et al., 2015b)) issues des données brutes qui permet d'extraire la composante statique de la gravité pour ne garder que la composante dynamique induite par les accélérations corporelles afin de classifier 4 types d'activités, à savoir l'inactivité, la marche, la course à pied (soit les activités ambulatoires) et toutes les activités « autres » (soit les activités non-ambulatoires), dont les algorithmes actuels ne permettent pas de détecter précisément le type d'activité réalisée.	Des accéléromètres 3D GT3x+ (ActiGraph®, Pensacola, FL, Etats-Unis) situés sur la hanche des participants ont été utilisés pour la première fois au cours d'un alitement prolongé afin de quantifier l'activité physique réalisée au cours de la période ambulatoire, ainsi que l'activité physique des participants au cours de la période d'alitement.	Des accéléromètres 3D GT3x+ (ActiGraph®, Pensacola, FL, Etats-Unis) situés sur la hanche des participants couplés à un enregistrement de la fréquence cardiaque ont été utilisés au cours de l'expédition afin de quantifier le coût de l'activité physique en milieu polaire. En effet, les accélérations corporelles faibles détectées par l'accéléromètre ne sont pas nécessairement associées à des activités d'intensité légère.

Résultats Expérimentaux

Chapitre 4. Regulation of energy balance during a 21-day bedrest with or without resistive exercise combined with vibration training: the MNX bedrest study

1. Résumé

Dans le contexte des missions de plus en plus longues, les agences spatiales développent des contremesures afin de prévenir des altérations induites par la microgravité ; l'exercice étant la pierre angulaire de ces contremesures. Les études d'alitement prolongé précédentes ont observé qu'une combinaison d'exercice aérobic et résistif induisait une augmentation de la DETJ non compensée par des apports énergétiques adaptés, résultant en une balance énergétique négative pouvant expliquer la perte de masse corporelle couramment observée au cours des vols spatiaux. Toutefois, l'effet d'un entraînement résistif seul sur la régulation de la balance énergétique reste méconnu. L'étude MNX, réalisée à la clinique de l'espace (Toulouse, France) en 2012-13 était un cross over permettant de comparer les effets de deux modalités de contremesure (exercice résistif + vibration, la vibration étant utilisée pour amplifier les bénéfices de la contraction musculaire sur le maintien de la masse musculaire) au cours d'un alitement prolongé (modèle terrestre analogue permettant de simuler les effets de la microgravité) de 21 jours à un alitement strict sur la régulation de la balance énergétique et la régulation de la composition corporelle chez 12 hommes adultes sains normo-pondérés. L'hypothèse était que la diminution de la DETJ due à l'inactivité physique ne serait pas différente entre les deux conditions, et n'impacterait pas la prise alimentaire permettant une balance énergétique stable. L'exercice permettrait par ailleurs de prévenir l'atrophie musculaire habituellement observée au cours des alitements prolongés sans contremesure.

La DETJ a été mesurée par eau doublement marquée pendant la période ambulatoire pré-alitement (7 jours) puis au cours de l'alitement prolongé (jour 1 à 9 et 10 à 21). Le MR et la composition corporelle ont été mesuré par calorimétrie indirecte et DEXA, respectivement, en période ambulatoire puis tous les cinq jours d'alitement, et la DEAP calculée avec l'équation DEAP= 0.9*DETJ – MR (0.1*DETJ correspondant à la TPP). L'accélérométrie 3D a également été utilisée pour mesurer l'activité physique au cours de l'alitement pour la première fois au cours d'une étude utilisant les modèles d'alitement prolongé. Les apports alimentaires étaient calculés selon les recommandations de l'agence spatiale européenne (apports prescrit = 1.4*MR + 0.1*DETJ), et ajustée en continue de façon à maintenir une MG stable. Toutefois, les participants étaient libres de ne pas finir leur repas ou demander plus de nourriture. Les restes ont été mesurés comme la différence entre les apports prescrits et ceux réellement consommés. L'entraînement résistif + vibration était réalisé deux fois par semaine sur un appareil permettant de réaliser des mouvements du membre inférieur (extension des genoux, flexions plantaires, etc.) couplés à une vibration (8mm pic à pic, 25Hz). La charge d'entraînement était calculée sur les performances mesurées pendant la période ambulatoire et ajustée (±5%) si l'exercice était trop simple / difficile. Au total, les participants ont réalisé six sessions d'environ 30 minutes.

La diminution de la DETJ due à l'inactivité physique induite par l'alitement prolongé n'était pas différente entre les traitements avec ou sans exercice. En d'autres termes, l'entraînement proposé n'impactait pas la DETJ ou ses composantes. La prise alimentaire n'était pas impactée non plus, avec une quantité de nourriture consommée proche des prescriptions, peu de restes alimentaires ou de demande de suppléments ayant été reportés. Bien que l'entraînement, basés sur des mouvements des membres inférieurs, ait limité la perte de masse des membres inférieurs dans le traitement exercice comparativement au traitement contrôle, cet effet ne s'appliquait pas au corps entier puisque la perte de masse corporelle totale n'était pas différente entre les groupes, principalement due à une perte de masse maigre. Ces résultats tendent à confirmer l'effet protecteur de l'exercice résistif combiné à la vibration pour limiter la perte de masse musculaire localement, sans affecter la régulation de la balance énergétique. Toutefois, les contremesures exercice doivent cibler l'ensemble des groupes musculaires afin de prévenir l'atrophie musculaire couramment observée en situation prolongée d'inactivité physique. Ainsi, les agences spatiales doivent trouver la modalité optimale qui permettra de préserver un maximum de systèmes (i.e. cardiovasculaires, musculaires, osseux) sans induire de perturbation concomitante majeure de la balance énergétique.

2. Manuscrit

Resistive exercise combined with vibration training preserve energy balance but is not sufficient to prevent bedrest-induced fat-free mass loss

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Abstract

Background: Exercise countermeasure is used to prevent spaceflight-induced physiological alterations including muscle atrophy. Previous bedrest studies suggested that high volumes of exercise lead to reduced body mass (BM) and fat mass (FM) due to maladjustments of energy intake (EI) to total energy expenditure (TEE). Negative energy balance (EB) can have health consequences for long-term missions. Because resistive exercise has minor impact on TEE, we tested the hypothesis that resistive + vibration exercise (RVE) mitigates the negative effect of bed-rest on muscle mass without altering the regulation of EB, BM and FM.

Methods: Twelve healthy young male were studied during 21 days of bedrest with RVE and without (CNT) in a randomized cross-over trial. Participants were encouraged to completely eat meals that matched their estimated TEE but were free to eat less. TEE and its components were studied at baseline and during bedrest using doubly labelled water and indirect calorimetry. Body composition was measured by dual X-ray absorptiometry (DXA). EB was estimated from body energy stores changes.

Results: The 21-day bedrest decreased BM (-4%, *P*<0.001) and fat-free mass (FFM) (-5%, P<0.001); FM was maintained. RVE partially prevented bedrest-induced decreases in both BM (estimated trial difference at the end of the bedrest RVE vs CNT [ETD] 0.79 kg, 95%CI -0.07 to 1.65, P=0.07) and FFM (ETD 0.71 kg; 95%CI -0.07 to 1.49, P=0.07). Bedrest reduced TEE adjusted for FM and FFM (RVE: -1.35 MJ/day [SE 0.34]; CNT: -1.83 [0.35]; P<0.001) in association with decreased AEE (P<0.001) and RMR (P<0.001). RVE partially prevented the changes in RMR (ETD = 0.17 MJ/d; 95%CI 0.00 to 0.34; P=0.06), but not in adjusted-AEE (ETD = 0.27 MJ/d; 95%CI -0.58 to 1.13; P=0.52). The decrease in adjusted EI was adapted to the lower TEE (-1.83 MJ/day [0.16] for RVE; -1.98 [0.17] for CNT; bedrest P<0.001). RVE had no effect on EI (P=0.48) and EB (RVE: -0.23 MJ/day [0.34]; CNT: -0.41 [0.36]; P=0.73).

Conclusion: Compared to strict bedrest, RVE partially protected FFM and RMR without inducing significant increases in AEE and TEE. It was associated with a matching decrease in EI and stable FM, which indicates an effective regulation of EB.

Introduction

Body mass (BM) loss is a common threat observed during spaceflight (Matsumoto et al., 2011). It indicates a negative energy balance, *i.e.* energy intakes lower than energy needs. Chronic negative energy balance can exacerbate the deleterious effects of microgravity, *i.e.* muscle atrophy, loss of bone mass, cardiovascular deconditioning, but also deterioration of mood and well-being (Bergouignan et al., 2016). Given the foreseen long-term missions (*e.g.* towards the Moon and Mars) (Bergouignan et al., 2016; Douglas et al., 2020), roadmaps for planetary exploration ranked energy balance management to a critical level. This requires to understand its regulation under microgravity conditions.

Negative energy balance can either be due to insufficient energy intakes (EI), high total daily energy expenditure (TEE), or both. By measuring free-living TEE with the gold standard doubly labelled water (DLW) method in astronauts before and after at least three months spent onboard the International Space Station, we demonstrated that TEE was directly related to overall physical activity (PA), *i.e.* the combined aerobic and resistive exercise training countermeasure coupled with daily activities (Bourdier et al., 2022b). We further showed that the energy requirements of the most active astronauts were not met by adequate intakes. This uncoupling between EI and TEE induced a negative energy balance, hence loss of fat mass (FM). The high levels of physical activity were however associated with a maintenance of fat-free mass (FFM). In contrast, the least active astronauts were in positive energy balance despite EI being below the prescriptions. While they achieved FM maintenance, they lost FFM (Bourdier et al., 2022b). These data obtained in space showed that performing exercise at significant volume may not be accompanied by compensatory changes in EI to match energy requirements, resulting in energy deficit.

These inflight data confirmed data previously obtained on Earth. In 2005, the Women International Space Simulation for Exploration (WISE) study tested the preventive effects of a countermeasure combining aerobic and resistive exercise, similar to the training protocols prescribed in space, during a 60-day head-down tilt (HDT) bedrest study, in female adults who were fed *ad libitum* (Bergouignan et al., 2010). Participants in strict bedrest without exercise countermeasure were close to energy balance thanks to a spontaneous reduction in EI that matched the lower TEE. This resulted in stable FM, but FFM was reduced due to muscle disuse (Bergouignan et al., 2010). As expected, participants who performed the exercise countermeasure maintained higher DLW-derived TEE than those in the strict bedrest control condition. But simultaneously, an excessive and non-adapted reduction in EI was observed that led to a negative energy balance and loss of FM. Of note, despite the combination of the two training modalities at high volumes, FFM was only partially protected. On the other hand, a training protocol based on resistive exercise only (flywheel ergometer, 35 min/d, 3-4 days/week) allowed to maintain FFM following a 2-month bedrest in male participants (Bergouignan et al., 2006), with no concomitant decrease in FM. Taken together these data suggest that, contrary to a training protocol that combines aerobic and resistive exercise, resistive exercise alone or combined with vibration (to stimulate muscle through involuntary contractions) may effectively prevent FFM loss while not adversely impacting energy balance regulation. This hypothesis has however never been rigorously tested.

The purpose of this study was to test the effects of a resistive exercise vibration (RVE) countermeasure to mitigate the negative effect of 21 days of bedrest on muscle mass. We hypothesized that the limited RVE impact on AEE and TEE, as measured by DLW coupled to indirect calorimetry, will not significantly alter energy balance and FM regulation.

Material & Methods

Participants

Twelve healthy men, volunteered to participate in the Medium Duration Nutrition and Resistance-Vibration Exercise (MNX) bedrest study, a 21-day, three-arm randomized, crossover study sponsored by the European Space Agency (ESA). The study was conducted in 2001-2002 at the Space Clinic MEDES located in Hospital Rangueil, Toulouse, France. Because our purpose was to study the effects of RVE *per se* on energetic and body composition outcomes, this analysis was conducted on data of the RVE and the control (CNT) trials only, and excluded the third cross-over arm that combined RVE with nutritional supplementation. One participant dropped after the first trial and did not participate in the CNT trial; therefore, the analysis was conducted with data collected in 12 participants in the RVE trial and 11 participants in the CNT trial.

All participants underwent a comprehensive screening protocol and gave their written informed consent. Inclusion criteria were aged between 25 and 45, body mass index (BMI) of 20-26 kg/m^2, being moderate active and VO_2 peak of 35-60 ml/min/kg if <35 years old, or 30-60 ml/min/kg if >35 years old. Other details about participants' inclusion and exclusion criteria were previously published (Cvirn et al., 2015; Kermorgant et al., 2019). Ethical approval was obtained from the Comité de Protection des Personnes / CPP Sud-Ouest Outre-Mer I) and French Health Authorities (Agence Française de

Sécurité Sanitaire des Produits de Santé) under the IDRCB n°2012-A00337-36. It observed the principles stated by the Declaration of Helsinki of 1898.

Overall study design

Study protocol was a randomly assigned crossover design during which all the volunteers were asked to complete 21-days of both CNT and RVE trials separated by a washout period of at least 4 months. The CNT trial required volunteers to always remain in supine position with at least one shoulder on the bed. The RVE trial was similar except volunteers were asked to perform six sessions of RVE. Participants resided at the MEDES testing facility for a 7-day period before each trial to standardize preparation and allow baseline data collection (BDC). Because this study was part of an ESA project, the volunteers were in -6° head down tilt position for the 21-day duration of bedrest (HDT) to mimic the vascular changes that are associated with microgravity. During BDC, participants were asked to stay moderately active by performing at least one daily aerobic or resistive exercise session per day and moving inside the MEDES building.

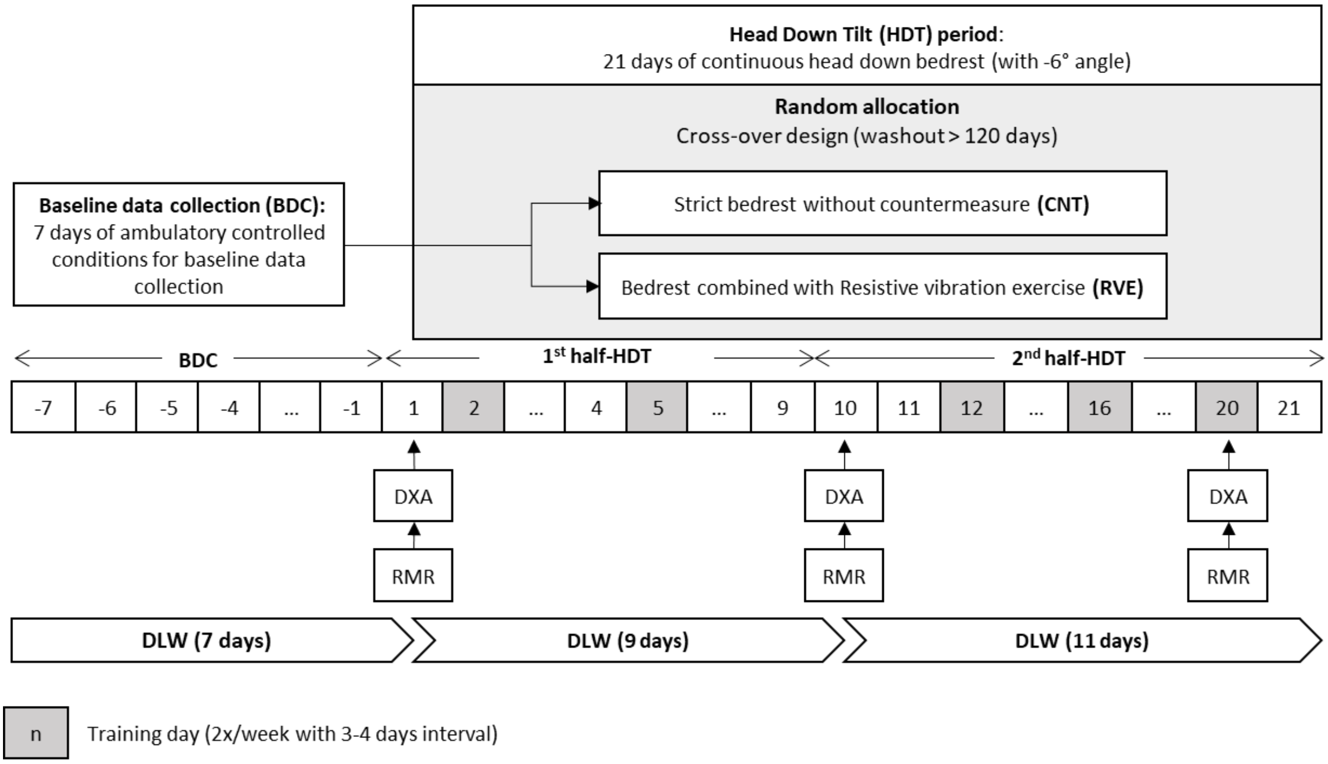

Figure 1: Schematic representation of the study general organization.
RMR= resting metabolic rate measurements; DXA= dual X-ray absorptiometry; DLW= period of measurement of total energy expenditure with the doubly labelled water (DLW) method.
BDC= ambulatory period from BDC-7 to HDT1; 1st half-HDT= bedrest period from HDT1 to HDT9; 2nd half-HDT= bedrest period from HDT10 to HDT21.
CNT= Control; RVE= resistive + vibration exercise (training days are shaded in light grey).

Resistive and vibration exercise countermeasure

The exercise training 30-min sessions were performed twice a week, *i.e.* on HDT 2, 5, 9, 12, 16 and 20 (**Figure 1**), using an integrated training device (Novotec Medical, Pforzheim, Germany). This device combines a standard leg press machine with a vibration platform (Galileo Sensor; 8mm peak-to-peak vibration at 25 Hz) located on the foot plate as previously used during the Berlin bedrest studies (Belavy et al., 2010). The exercise training was previously published (Guinet et al., 2020; Kenny et al., 2017). Briefly, participants performed bilateral squats and single heel raises or bilateral heel raises. The initial load was determined based on participants' one repetition maximum (1-RM), and a 5% adjustment was made based on their ability to complete the set of exercises.

Body mass and composition

BM and body composition were measured throughout the bedrest in fasting participants in underwear. BM was measured daily using a calibrated scale designed to weight persons in bed-rested position. Fat mass (FM) and fat-free mass (FFM) were assessed by dual-energy x-ray absorptiometry (DXA, Hologic QDR-4500C) and its companion software version 11.2 (Hologic, Inc., Marlborough, MA, USA) at BDC-7 and HDT1 (pre-bedrest), HDT10 and HDT 20 during the bedrest.

Energy components and balance

Total energy expenditure

TEE was determined over three consecutive periods: during baseline (from BDC-7 to HDT1), and during the first half (from HDT1 to HDT9) and the second half (HDT10 to HDT21) of the bedrest using the doubly labelled water (DLW) method (**Figure 1**) as previously described (Schoeller, 1988).

During each trial, participants received three DLW doses: a 2.00 g/kg of estimated total body water (TBW) premixed dose, composed of 0.20 g/kg TBW $H_2{}^{18}O$ enriched at 10% and of 0.15 g/kg TBW ^2H_2O enriched at 99% (Eurisotop, Saint-Aubin, France) at BDC-7; a 1.60 g/kg TBW premixed dose composed of 0.16 g/kg TBW $H_2{}^{18}O$ and of 0.12 g/kg TBW ^2H_2O at HDT 1 and a 1.30 g/kg TBW premixed dose composed of 0.13 g/kg TBW $H_2{}^{18}O$ enriched at 10% and 0.10 g/kg TBW of ^2H_2O enriched at 99% at

HDT10. Doses were calculated to obtain a maximal enrichment of 150 ppm for ^{18}O and 130 ppm for ^{2}H after each of the 3 successive DLW ingestions. For each of the 3 periods, urines were collected before, and 4 and 5 hours after dose ingestion to calculate equilibration (Blanc et al., 2002). Urines of the second void were then daily collected until the end of the measurement period to calculate TEE using the multi-point DLW approach (Cole & Coward, 1992). Urines were cleaned with black carbon and filtered to extract water, as previously described (Chery et al., 2015). Hydrogen and oxygen isotope ratios were measured using a high-temperature conversion elemental analyzer (TC/EA) interfaced with a Delta V Plus Isotope-Ratio Mass spectrometer and a Conflo III interface (THERMO, Bremen, Germany). Analyses were performed in quadruplicate and repeated if the SD exceeded 2% for deuterium and 0.2% for 18-oxygen.

The dilution spaces for ^{2}H and ^{18}O were calculated from the baseline and equilibration samples according to Coward et al. (Coward et al., 1994). ^{2}H and ^{18}O constant elimination rates were calculated by least-squares linear regression on the natural logarithm of isotope enrichments from all urine samples as a function of elapsed time from dose administration. CO_2 production was then calculated according to Schoeller et al. (Schoeller, 1988) modified by Racette et al. (Racette et al., 1994), and TEE derived using Weir’s formula (Weir, 1949) using food quotient from actual food intakes (Black et al., 1986).

Resting metabolic rate and activity-related energy expenditure

RMR was measured by indirect calorimetry (Deltatrac II, Datex-Ohmeda, Madison, WI, USA) for 45 min and after overnight fast at the beginning of each of the three TEE measurement periods and at the end of the bedrest (**Figure 1**). Oxygen consumption and carbon dioxide production were continuously recorded using a ventilated hood (canopy). RMR was calculated using the Weir’s formula (Weir, 1949). For each TEE measurement, the average of RMR measured at the beginning and at the end of the DLW corresponding period was calculated. Physical activity-related energy expenditure (AEE) was calculated as $TEE \times 0.9 - RMR$, assuming a diet-induced thermogenesis (DIT) of 10% TEE. PA level (PAL) was calculated as the ratio between TEE and RMR.

Time spent sedentary and physically active was further determined using a tri-axial accelerometer (ActiGraph GT3X+; ActiGraph, Pensacola, USA). Participants were instructed to wear the accelerometer at their right hip 24h a day throughout the experimental trials. Vector magnitude counts per min

(VMCPM), steps and raw acceleration were downloaded using the manufacturer'software (ActiLife version 6.4). After identification of sleep and non-wear time, an automatic activity-recognition algorithm (Bastian et al., 2015) was used to determine time spent in different postures and activities, and in activities of different intensities (Garnotel et al., 2018). Valid days were defined as at least 10h wear-time during waking time. Sedentary behavior was defined as the time spent awake in lying, reclining or sitting postures. A cutpoint of 3 METs was used for moderate-to-very vigorous activity. VMCPM was further used as an indicator of overall PA throughout the experimental trials.

Energy intake

Prescribed daily EI was adjusted to match energy expenditure throughout the trials to maintain energy balance and FM (from DXA), using a macronutrient composition of a 30% fat, 1.2 g/kg protein and about 55% carbohydrates. Initial prescribed EI were 155% and 125% RMR (including 10% of TEE for DIT), respectively for baseline and bedrest periods. An additional EI prescription of 280 kJ/d was added in the RVE group during bedrest to account for the energy cost of RVE. Meals were provided quick-frozen by an industrial manufacturer (Davigel, France) and prepared in the metabolic kitchen of the MEDES. Nutritional values were calculated by the Nutrilog software®. Food quotient was derived using Black's formula (Black et al., 1986).

Participants were encouraged to completely eat the offered daily meals but free to eat less. Actual EI was quantified from prescribed EI and leftovers.

Energy balance

Changes in energy stores throughout the full bedrest period were calculated using equations proposed by Ravelli & Schoeller (Ravelli & Schoeller, 2021).

Statistical analysis

Baseline characteristics are presented as means (standard deviation [SD]). Otherwise indicated, data are presented as least squared means (LSmeans) with their standard error (SE) or 95% confidence interval (CI).

Linear mixed-effects models accounting for repeated measures among and throughout the trial periods were used to test the effect of RVE on the bedrest-induced changes on the anthropometric and energetic outcomes. Trial, time and their interactions were included as fixed effects in the models as well as campaign and sequence (*i.e.* order of the trials) to account for the cross-over design. A subject-specific random intercept was added for between-subject heterogeneity, and an autoregressive or a compound-symmetric covariance structure (based on the smallest information criteria) was used to account for the dependencies among measurements throughout trial periods. Our statistical inference was the estimated between-trial differences (ETD, RVE vs CNT) in outcome net changes (HDT20, *i.e.* end of the bedrest, vs BDC) estimated with their 95% confidence interval (CI). Additional adjustment on both FFM and FM was done for TEE, AEE and RMR. Normality of the model residuals was checked using a residual plot.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) with a two-sided 5% significance level. No statistical adjustment was made for multiple comparisons as the purpose of this study remained exploratory. The *a-posteriori* power to detect an ETD between HDT21 and BDC for TEE of 1 MJ/day was 0.54. Figures were realized with Prism 9.3 (GraphPad, San Diego, California)

Results

Characteristics of the participants

Initial characteristics of the participants are presented in **Table 1**. They were on average 34.3 years old (range 29 to 44), had a BMI of 22.6 kg/m² (SD 1.9) and an FFM index (FFMI) of 18.2 kg/m² (1.3). They were selected to be moderately active and fit with a mean VO_2 peak of 37.4 ml/min/kg (4.1). During baseline ambulatory period they spent 46 min/d (8) in ambulatory activities, 790 min/d (123) in sedentary activities, and 36 min (11) min/d in MVPA.

Table 1: Initial characteristics of the participants (n=12).

	Baseline	
	Mean (SD)	**Minimum - maximum**
Anthropometric variables		
Height (m)	1.76 (0.06)	1.72 – 1.79
Body mass (kg)	70.2 (8.9)	64.6 – 75.9
Fat mass (kg)	13.5 (4.3)	10.8 – 16.2
Fat-free mass (kg)	56.7 (6.9)	52.3 – 61.1
Body mass index (kg/m²)	22.6 (1.9)	21.3 – 23.8
Fat mass index (kg/m²)	4.3 (1.3)	3.5 – 5.2
Fat-free mass index (kg/m²)	18.2 (1.3)	14.4 – 19.0
Cardio-respiratory variables		
VO_2max (ml/min)	2603 (405)	2345 – 2860
VO_2max (ml/min/kg)	37.4 (4.1)	34.8 – 40.0
Accelerometric variables		
Steps (n/day)	3992 (642)	3532 - 4451
Moderate-to-vigorous physical activity (min/day)	36 (11)	28 – 44
Sedentary time (min/day)	790 (123)	702 - 878
Ambulatory activities (min/day)	46 (8)	41 – 52

Values are means (SD).

Effects of the RVE treatment on anthropometric outcomes during bedrest

As illustrated in **Table 2** and **Figure 2**, BM progressively decreased during bedrest (P<0.001) in association with a decrease in FFM (RVE -2.25 kg [0.27]; CNT -2.97 kg [0.28]; bedrest P<0.001). RVE partially prevented bed-rest induced changes in both BM (estimated trial difference vs CNT at HDT20 [ETD] 0.79 kg; 95%CI -0.07 to 1.65; P=0.07) and FFM (ETD 0.71 kg; 95%CI -0.07 to 1.49; P=0.07). FM slightly increased during bedrest (RVE 0.19 [0.19]; CNT 0.11 [0.20] kg; bedrest P<0.01) with no effect of RVE.

Table 2: Changes in anthropometric, energetic and accelerometer-derived physical activity outcomes during a 21-day bedrest.

	Baseline		Mid bedrest		End bedrest		Bedrest	ETD in end-changes from baseline		
	CNT	**RVE**	**CNT**	**RVE**	**CNT**	**RVE**	**P**	**LS means (SE)**	**95%CI**	**P**
Anthropometric variables										
Body mass (kg)	70.7 (2.1)	70.7 (2.1)	-1.52 (0.22)	-1.18 (0.21)	-2.85 (0.31)	-2.06 (0.29)	<.001	0.79 (0.43)	-0.07 to 1.65	0.069
Fat mass (kg)	14.3 (1.1)	14.0 (1.1)	-0.18 (0.14)	-0.15 (0.14)	0.11 (0.20)	0.19 (0.19)	0.004	0.08 (0.28)	-0.48 to 0.64	0.780
Fat-free mass (kg)	56.5 (1.8)	56.7 (1.8)	-1.35 (0.23)	-1.03 (0.22)	-2.97 (0.28)	-2.25 (0.27)	<.001	0.71 (0.39)	-0.07 to 1.49	0.073
Body mass index (kg/m^2)	22.7 (0.5)	22.7 (0.5)	-0.49 (0.07)	-0.38 (0.07)	-0.91 (0.10)	-0.66 (0.09)	<.001	0.25 (0.14)	-0.02 to 0.53	0.072
Fat mass index (kg/m^2)	4.6 (0.4)	4.5 (0.3)	-0.06 (0.05)	-0.05 (0.04)	0.04 (0.06)	0.05 (0.06)	0.003	0.01 (0.09)	-0.17 to 0.19	0.892
Fat-free mass index (kg/m^2)	18.1 (0.4)	18.2 (0.4)	-0.43 (0.07)	-0.33 (0.07)	-0.95 (0.09)	-0.71 (0.08)	<.001	0.24 (0.12)	-0.00 to 0.49	0.053
Energetic variables										
Non-adjusted										
Total energy expenditure (MJ/d)	11.0 (0.4)	10.9 (0.4)	-1.72 (0.34)	-1.88 (0.33)	-2.09 (0.34)	-1.57 (0.33)	<.001	0.52 (0.47)	-0.44 to 1.47	0.279
Resting metabolic rate (MJ/d)	6.5 (0.2)	6.5 (0.2)	-0.25 (0.05)	-0.19 (0.04)	-0.44 (0.06)	-0.25 (0.06)	<.001	0.19 (0.08)	0.02 to 0.36	0.026
Activity energy expenditure (MJ/d)	3.4 (0.3)	3.4 (0.3)	-1.30 (0.31)	-1.50 (0.29)	-1.44 (0.31)	-1.17 (0.29)	<.001	0.27 (0.42)	-0.58 to 1.13	0.520
Actual energy intake (MJ/d)	10.1 (0.3)	10.2 (0.3)	-1.98 (0.15)	-1.76 (0.15)	-2.21 (0.15)	-2.02 (0.15)	<.001	0.19 (0.21)	-0.24 to 0.61	0.378
Adjusted										
Total energy expenditure (MJ/d)	10.9 (0.3)	10.8 (0.3)	-1.63 (0.34)	-1.80 (0.33)	-1.83 (0.35)	-1.35 (0.34)	<.001	0.48 (0.47)	-0.48 to 1.44	0.315
Resting metabolic rate (MJ/d)	6.4 (0.15)	6.4 (0.2)	-0.19 (0.05)	-0.14 (0.05)	-0.29 (0.08)	-0.12 (0.08)	<.001	0.17 (0.09)	0.00 to 0.34	0.056
Activity energy expenditure (MJ/d)	3.4 (0.26)	3.4 (0.3)	-1.29 (0.31)	-1.50 (0.29)	-1.40 (0.31)	-1.13 (0.30)	<.001	0.27 (0.42)	-0.58 to 1.13	0.523
Actual energy intake (MJ/d)	10.1 (0.2)	10.1 (0.2)	-1.90 (0.15)	-1.69 (0.15)	-1.98 (0.17)	-1.83 (0.16)	<.001	0.15 (0.21)	-0.27 to 0.58	0.475
Accelerometric variables										
Vector magnitude (cpm/day)	385960 (12554)	387831 (11648)	-264885 (14073)	-275327 (13062)	-280591 (14794)	-283807 (13062)	<.001	-3215 (19735)	-42906 to 36475	0.871

Steps (number/day)	4324 (136)	4403 (124)	-3970 (182)	-4047 (169)	-3994 (191)	-4056 (169)	<.001	-62 (255)	-574 to 451	0.810
Moderate-to-vigorous physical activity (min/day)	41 (2)	38 (2)	-41 (3)	-38 (3)	-41 (4)	-38 (3)	<.001	3.0 (4.7)	-6.3 to 12.4	0.517
Sedentary time (min/day)	799 (40)	752 (37)	394 (60)	437 (56)	396 (52)	490 (44)	<.001	94.1 (68.0)	-44.5 to 232.6	0.176
Ambulatory activities (min/day)	52 (2)	48 (2)	-51 (3)	-48 (3)	-51 (3)	-48 (3)	<.001	3.4 (4.3)	-5.2 to 12.0	0.436

Values are LS means (SE).

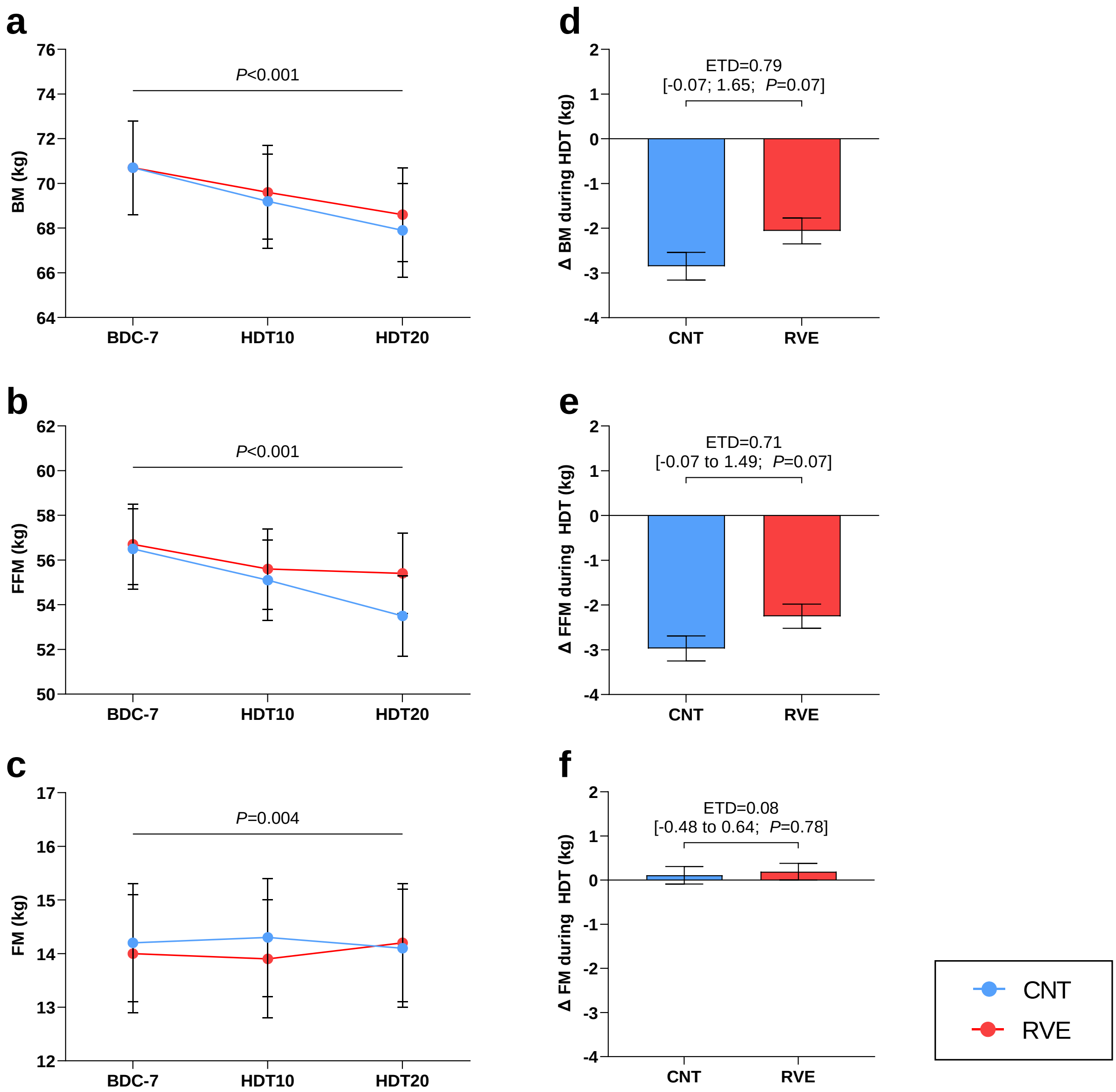

Figure 2: Changes in body mass and composition during a 21-day bedrest with or without an RVE countermeasure.
Values are LS means (SE) from linear mixed-effects model accounting for repeated measurements (a to c), and estimated trial-differences (ETD) (d to f) presented with their 95% confidence interval (95%CI).
BM= Body mass; FFM= fat-free mass; FM= Fat mass.

Effects of the RVE treatment on energetic and physical activity outcomes during bedrest

Bedrest induced a decrease in TEE (**Table 2** and **Figure 3**) occurring from the first-half period of bedrest. The decrease in TEE remained significant after adjustment on FM and FFM (RVE: -1.35 MJ/day [SE 0.34] during the 2nd half-period; CNT: -1.83 [0.35]; bedrest P<0.001) and was related to a decrease in both AEE (P<0.001) and RMR (P<0.001). RVE partially prevented the bedrest-induced drop in adjusted RMR (ETD 0.17 MJ/d; 95%CI 0.00 to 0.34; P=0.06) but not in adjusted AEE (ETD 0.27 MJ/d; 95%CI -0.58 to

1.13; P=0.52). Accelerometry further detected the dramatic drop during bedrest in steps, ambulatory activities and VMCPM, an indicator of overall PA, while sedentary time increased with no difference between the two trials.

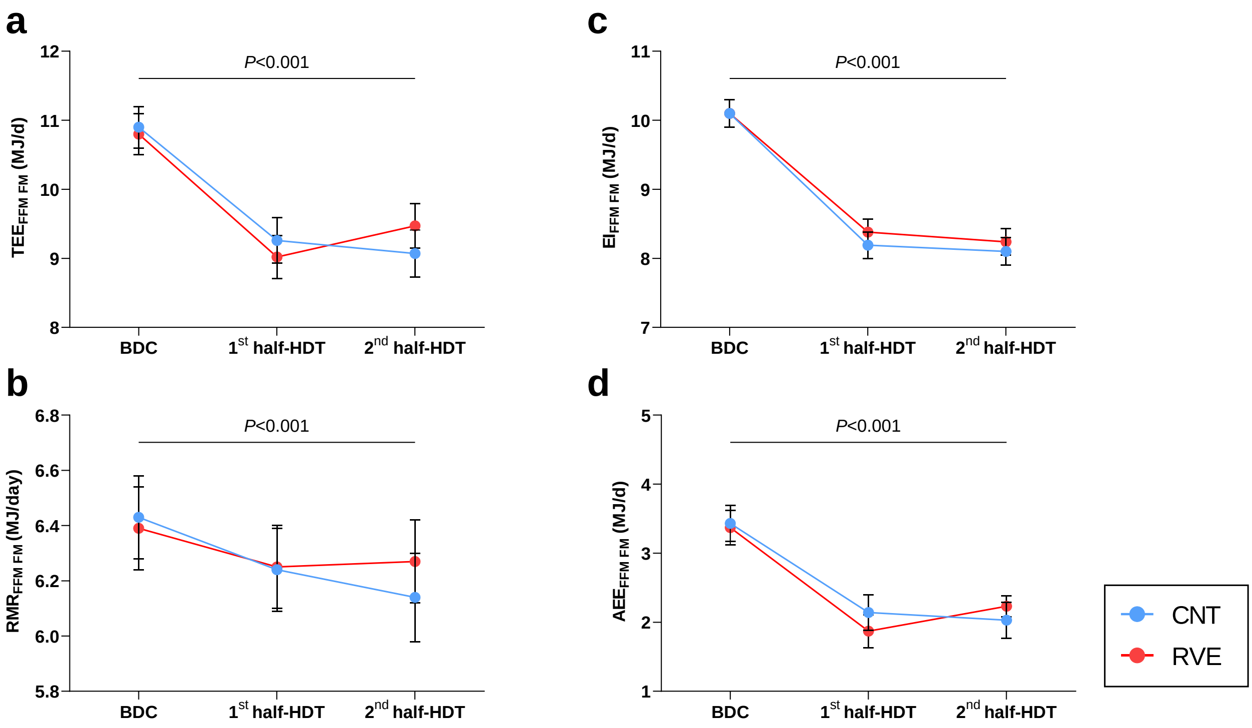

Figure 3: Changes in energetic outcomes during the 21-day bedrest with or without an RVE countermeasure.
Values are LS means (SE) from linear mixed-effects model accounting for repeated measurements.
BDC= ambulatory period from BDC-7 to HDT1; 1st half-HDT= bedrest period from HDT1 to HDT9; 2nd half-HDT= bedrest period from HDT10 to HDT21.
$TEE_{FFM\ FM}$= total energy expenditure adjusted; $AEE_{FFM\ FM}$= activity-related energy, $RMR_{FFM\ FM}$= resting metabolic; $EI_{FFM\ FM}$= energy intakes. Values are adjusted for adjusted for FFM and FM.

Effects of the RVE treatment on energy intakes and energy balance

Although prescribed EI was calculated to match the decreased TEE during bedrest (including the cost of RVE training), participants were free to eat less. The decrease in EI adjusted for FM and FFM followed a similar pattern than the decrease in TEE (RVE: -1.83 MJ/day [0.16] during the 2nd half-period; CNT: -1.98 [0.17]; bedrest P<0.001). RVE had no effect on either the changes in adjusted EI (P=0.48) (**Table 2** and **Figure 3)** or energy balance, as calculated from body composition over the whole bedrest-period (RVE: -0.23 MJ/day [SD 0.34]; CNT: -0.41 MJ/d [0.36] for CNT; *P*=0.73) (**Figure 4**).

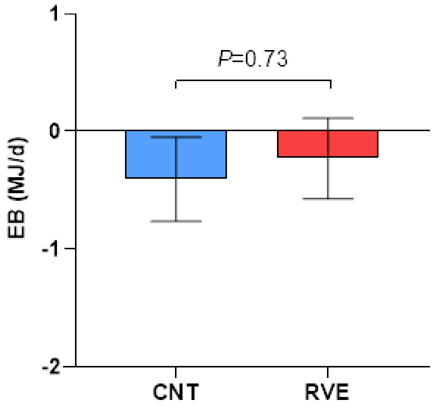

Figure 4: Energy balance (EB) calculated from TEE, EI and changes in body composition during the 21-day bedrest for CNT and RVE trials.
Values are means (SD) during the full HDT period.

Discussion

Exercise is the cornerstone of the countermeasures program aiming to preserve astronauts' health and performance during space missions. However, high volumes of combined aerobic and resistive exercise training are not necessarily fully preventing FFM loss while inducing negative energy balance, which can detrimentally affect astronaut's health during long term planetary missions (Bourdier et al., 2022b). While previous data suggested that resistive exercise may overcome these issues by maintaining FFM without altering the regulation of energy balance, this hypothesis had never been tested. This study confirmed that RVE treatment does not alter the coupling between EI and TEE, which allows the maintenance of stable energy balance over 21-days of bedrest. However, contrary to our hypothesis, RVE was not efficient at maintaining FFM.

From an energetic standpoint, RVE appears as an interesting strategy as it had limited and not significant impact on TEE. It further did not alter energy balance contrary to an aerobic or a combined aerobic/ resistive exercise training (Bergouignan et al., 2010; Laurens et al., 2019). Rapid decreases in TEE (mostly through the physical inactivity-induced drop in AEE) happened in both trials between BDC and the first half start of bedrest, then remained relatively stable as previously described (Bergouignan et al., 2010; Stein et al., 1999b). These data are supported by a drop in accelerometry-derived VMCPM (a proxy of overall PA) at the onset of the bedrest period, with no between-treatment difference. RMR also decreased during bedrest, even after adjusting for both FM and FFM, with only a partial preventing effect of RVE. A decrease in RMR was previously observed during bedrest studies with no exercise countermeasure (Molé, 1990). While a decrease of about 10% was commonly described, the use of exercise training achieved to maintain stable RMR (Molé, 1990). This suggests that RVE training did not induce a sufficient stimulus to maintain RMR.

EI prescriptions were regularly adapted during the bedrest to ensure FM balance. While participants were not fed *ad* libitum, they were allowed to not finish their meal, however, very few leftovers were reported. This suggests that prescriptions were adapted to the requirements of this specific countermeasure, and that appetite was not altered during the 21-day bedrest with or without the RVE treatment. Of note, appetite sensations were not measured in the present study. This coupling between TEE and EI was previously reported in the control group (strict bedrest) during the WISE bedrest study (Bergouignan et al., 2010). In contrast, in this latter study, the reduction in EI was greater than the reduction in TEE in the aerobic/resistive exercise group resulting in FM loss (Bergouignan et al., 2010). This suggested an anorexigenic effect of the combined aerobic and resistive exercise training as previously observed in space (Bourdier et al., 2022b). The beneficial effects of RVE on energy metabolism should also be acknowledged since it was shown to mitigate the bedrest-induced development of insulin resistance, impaired mitochondrial metabolism, protein synthesis and degradation pathways, hence leading to specific protective effects (Kenny et al., 2017; Kenny et al., 2020).

Contrary to our hypothesis, the RVE used in this study was not sufficient to fully prevent total BM nor FFM loss. This was already reported by Kenny et al. (Kenny et al., 2017). This bedrest-induced adaptation is likely the result from insufficient physical activity workload, as previously observed during long-term spaceflights where the least active astronauts lost FFM while achieving FM maintenance (Bourdier et al., 2022b). In parallel, participants using a flywheel-based resistive training in the 90-day LTBR study in male adults achieved FFM and FM maintenance (Bergouignan et al., 2006). Differences in exercise protocols may explain these results and require additional research.

Considering all those data together, high intensity interval training (HIIT) combining both resistive and aerobic exercise may be an interesting alternative as it may overcome the limitations of the currently used and tested exercise countermeasures. Indeed, Matsuo et al. (Matsuo et al., 2012a; Matsuo et al., 2012b) showed that a HIIT protocol performed on ergocycle was associated with lower energy expenditure than a continuous ergocycle exercise currently performed by astronauts onboard the International Space Station. However, this finding should be considered with caution given that it was difficult to precisely match both exercise modalities for session duration or total workload (Andreato et al., 2019; Kruel et al., 2009). In addition, the effects of HIIT on appetite sensation or food intake remain complex and nuanced due to individuals' and training's characteristics (Chen et al., 2022; Hu et al., 2023). These limitations require a specific focus for the prescription of exercise countermeasure during long-term spaceflight, especially given that a space anorexia is commonly reported during these missions (Da Silva et al., 2002).

Taken altogether, these findings suggest that RVE does not impair energy balance. However, further studies are needed to test i) an increased total workload with adequately stimulated muscles to fully prevent FFM loss, and ii) target whole-body exercises as currently prescribed onboard the International Space Station to optimize the benefits of training.

Finally, strengths and limitations should be acknowledged. While previous studies showed that acute exercise associated with vibrations increases energy expenditure above resting levels (Bertucci et al., 2015; Da Silva et al., 2007), no information existed on the impact of this exercise modality on TEE over longer periods of time (*i.e.* day to week). This was the first study to objectively and accurately measure TEE and its components by combining the gold standards methods of DLW and indirect calorimetry. A limitation is the number of participants that may have limited statistical power to detect significant between-trials differences in TEE. However, what matters is that the impact of RVE on TEE was modest and did not alter EI, energy balance and FM maintenance. Another limitation of this study was related to food prescription. Although participants were allowed to eat less food than what they were given, food was not provided *ad libitum* and participants were not allowed to ask for more. Neither appetite sensation nor gut hormones were measured in the present study, thus limiting the complete interpretation of the impact of RVE on food intake regulation. Finally, participants were males only, thus these results may not apply to females.

Conclusion

Resistive exercise coupled with vibrations aiming at increasing muscle contractions through reflex loops was tested to mitigate microgravity-induced BM and FFM loss and thus preserve functions. While this exercise countermeasure does not impair energy balance regulation, it only partially preserved FFM. If the observed alterations are extended to current spaceflight duration (*i.e.* around 6 months), they may have deleterious consequences on muscle function and hence, physiological and operational functions. Further studies are required to optimize exercise countermeasures to protect astronaut’s health.

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Chapitre 5. Effects of exercise on energy expenditure and body composition in astronauts onboard the International Space Station: Considerations for interplanetary travel

1. Résumé

Si les modèles analogues terrestres permettent de mieux comprendre les effets de la microgravité sur la régulation de la balance énergétique, ils demeurent toutefois imparfaits puisqu'ils ne représentent pas les conditions de vie réelle au cours des missions spatiales. Malgré des apports prescrits basés sur les besoins théoriques et un entraînement physique adapté pour prévenir des adaptations induites par la microgravité, la perte de masse reste au cœur des préoccupations des agences spatiales. Plus spécifiquement, les données collectées au cours des différentes missions ont montré que les pertes de masse étaient plus importantes dans les astronautes pratiquant un volume d'exercice important, suggérant un rôle majeur de l'exercice dans la régulation de la dépense énergétique. L'étude exploratoire ENERGY avait pour but d'estimer les besoins énergétiques des astronautes à bord de l'ISS en prenant spécifiquement en compte l'impact de l'activité physique, ainsi que les changements de composition corporelle après plus de trois mois en vol. L'hypothèse était que l'activité physique en vol, principalement déterminée par l'entraînement, serait le principale déterminant des changements de masse et de composition corporelle.

Les données ont été collectées chez onze astronautes masculins sélectionnés par les agences spatiales américaine, canadienne, européenne et japonaise. Deux sessions de mesure similaires (au sol et après 3-5 mois de vol) ont été réalisées au cours desquelles la DETJ a été mesurée par eau doublement marquée et le MR par calorimétrie indirecte, permettant de déduire la DEAP. En plus d'être l'une des 4 études à utiliser l'eau doublement marquée au cours d'une mission spatiale, ENERGY était le premier protocole à proposer l'utilisation de capteurs multisensoriels (i.e. accélérométrie 2D, température cutanée, flux galvanique) couplés à des journaux d'activité afin de quantifier l'activité physique quotidienne (exercice + activités spontanées / relatives aux missions en vol). De plus, ENERGY a permis de mesurer la composition corporelle sur Terre, mais également en vol en utilisant la dilution isotopique, alors que l'ensemble des études ne proposaient qu'une évaluation pré / post-mission.

L'impact de l'activité physique en microgravité réelle confirme les résultats observés au cours des alitements prolongés avec des contremesures exercice. Si aucune modification de la DETJ ou de la masse et de la composition corporelles n'a été observée après plus de trois mois en vol chez les astronautes, les résultats d'ENERGY ont permis de mettre en évidence une forte variabilité inter-individuelle qui jusque-là n'avait jamais été montrée. Ainsi, si la moitié des astronautes de l'étude ont maintenu une DETJ stable en vol comparativement à celle mesurée au sol avant la mission, l'autre moitié à diminué sa DETJ. Sur la base de ces différences, deux groupes ont été construits a posteriori. Tandis que les astronautes du premier groupe ont maintenu une masse maigre stable au dépend d'une perte de masse grasse, ceux du deuxième groupe ont perdu de la masse maigre au profit d'une prise de masse grasse. Si la pratique d'exercice en vol apparait comme l'une des explications à ces différences (les astronautes les plus actifs passant plus de temps en exercice, principalement dans les activités de type aérobie), il est également important de prendre en compte la dépense liée aux activités spontanées de la vie quotidienne (déplacements à bord de la station, tâches de maintenance, etc.). En effet, les données dérivées de l'accélérométrie ont permis d'observer une baisse du temps passé en activités ambulatoires (i.e. marche et course) en condition de microgravité au profit d'une augmentation du temps passé dans les activités non-ambulatoires (i.e. toutes les activités détectées par l'appareil sauf la marche et la course). Par ailleurs, la pratique d'activité physique quotidienne sur Terre et la composition corporelle avant la mission apparaissent comme des facteurs déterminants des changements observés en vol. Ainsi, les astronautes les plus actif et musclés au sol restent les plus actifs et musclés en vol. Ces données soulignent l'importance de prendre en compte les caractéristiques individuelles des astronautes (pratique d'activité physique et composition corporelle) pendant mais également avant la mission afin d'optimiser les prescriptions en termes d'exercice ou d'alimentation. Une solution repose sur le développement méthodologique permettant de traquer en continu les changements de composition corporelle des astronautes, ou encore de suivre leurs apports et dépenses énergétique. Pour cette dernière, bien que l'eau doublement marquée permette de mesurer la DETJ, les composantes de la DEAP reste encore une boîte sombre puisque la nature des activités quotidiennes ne peut, à ce jour, pas être mesurée objectivement par objectivement. Or, elle reste le principale déterminant de la DETJ, et requiert une attention particulière, notamment dans l'optique des missions futures dont la durée est estimée à plusieurs années.

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ORIGINAL RESEARCH ARTICLE

Effect of Exercise on Energy Expenditure and Body Composition in Astronauts Onboard the International Space Station: Considerations for Interplanetary Travel

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Abstract

Objective Body mass (BM) loss and body composition (BC) changes threaten astronauts' health and mission success. However, the energetic contribution of the exercise countermeasure to these changes has never been investigated during long-term missions. We studied energy balance and BC in astronauts during 6-month missions onboard the International Space Station.

Methods Before and after at least 3 months in space, BM, BC, total and activity energy expenditure (TEE and AEE) were measured using the doubly labeled water method in 11 astronauts (2011–2017). Physical activity (PA) was assessed by the SensewearPro® activity-device.

Results Three-month spaceflight decreased BM (− 1.20 kg [SE 0.5]; $P=0.04$), mainly due to non-significant fat-free mass loss (FFM; − 0.94 kg [0.59]). The decrease in walking time (− 63.2 min/day [11.5]; $P<0.001$) from preflight was compensated by increases in non-ambulatory activities (+64.8 min/day [18.8]; $P<0.01$). Average TEE was unaffected but a large interindividual variability was noted. Astronauts were stratified into those who maintained (stable_TEE; $n=6$) and those who decreased (decreased_TEE; $n=5$) TEE and AEE compared to preflight data. Although both groups lost similar BM, FFM was maintained and FM reduced in stable_TEE astronauts, while FFM decreased and FM increased in decreased_TEE astronauts (estimated between-group-difference (EGD) in ΔFFMindex [FFMI] 0.87 kg/m^2, 95% CI+0.32 to+1.41; $P=0.01$, ΔFMindex [FMI] − 1.09 kg/m^2, 95% CI − 2.06 to − 0.11 kg/m^2; $P=0.03$). The stable_TEE group had higher baseline FFMI, and greater baseline and inflight vigorous PA than the decreased_TEE group ($P<0.05$ for all). ΔFMI and ΔFFMI were respectively negatively and positively associated with both ΔTEE and ΔAEE.

Conclusion Both ground fitness and inflight overall PA are associated with spaceflight-induced TEE and BC changes and thus energy requirements. New instruments are needed to measure real-time individual changes in inflight energy balance components.

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Key Points

Space agencies ranked energy balance control to critical level for human space exploration. Although exercise is a cornerstone of countermeasure programs to prevent microgravity-induced physiological alterations, the energy cost of physical activity during long-term spaceflights has never been studied.

Six-month missions on the International Space Station led to large inter-individual variability in body composition changes. Astronauts maintaining pre-flight total and activity energy expenditures (possibly due to both physical training and unexpected non-exercise activity) maintained fat-free mass but lost fat mass. Conversely those who decreased energy expenditures lost fat-free mass but gained fat mass. Fat mass changes reflects unmatched energy intake adaptation to expenditures during flight.

On average, astronauts who maintained energy expenditures during flight were also fitter on the ground.

The large between-astronauts variability suggests that energy requirements cannot be derived from general population equations. Methods to track inflight changes in body composition, energy intake and energy expenditure are needed to determine individual energy requirements to ensure astronaut's performance and mission success.

1 Introduction

The human spaceflight program has entered a new phase of space exploration directed towards the Moon and Mars. Space agencies have developed roadmaps that define research priorities enabling planetary exploration. Among those, understanding inflight energy balance regulation has been placed as a top priority, as energy homeostasis is vital for both medical and operational reasons. Any energy deficit will not only impact fat mass (FM), but it can also increase loss of bone and of muscle mass and strength, favor cardiovascular deconditioning, and impair numerous other physiological functions. Overall it conditions astronaut's performance and health, and ultimately may affect mission success [1].

A loss of body mass (BM) is a hallmark of spaceflights. On Mir (4 months) [2, 3], Shuttle (4–19 days) [4, 5] and early International Space Station (ISS) missions (128–195 days) [6, 7], astronauts lost more than 5% of their preflight BM despite sufficient food onboard with no clear relationship with mission duration [8]. In some cases, this loss even exceeded 10% of preflight BM, which is clinically significant. Conversely, BM was successfully maintained in few missions, such as SpaceLab Life Sciences Space Shuttle missions SLS1 and SLS2 in the 1990s [9] or, more recently, on the ISS [7, 10]. Yet, recent reports from the ISS show that astronauts still lose from 2 to 5% of their initial BM with a large between-subject variability [6, 11]. We recently hypothesized that an energy balance dysregulation, i.e., an uncoupling between energy intake (EI) and expenditure, occurs in space [8]. Very little data, however, exist to support this hypothesis.

The regulation of energy balance was measured with objective doubly-labeled water (DLW) methods in three studies during short-term spaceflights only [4, 9, 12]. The results of two of these studies indicate that energy balance is not optimal in space when exercise is performed, i.e., compensatory changes in EI are insufficient to match increases in energy expenditure [13]. During the 17-day Life and Microgravity Science (LMS) Space Shuttle mission, Stein et al. [4] observed in four astronauts an energy deficit as large as 5.7 MJ/day that was associated with the loss of up to 2 kg of fat mass (FM). Concomitantly, even though heavy exercise training was specifically prescribed during this mission to prevent loss of muscle mass and bone, astronauts presented a negative nitrogen balance indicating protein loss related to a maladjustment of energy and protein intakes to high requirements. By contrast, during the SLS1 and SLS2 missions, during which no exercise was prescribed, the astronauts maintained stable energy balance with only a moderate negative nitrogen balance likely thanks to the maintenance of protein intakes despite an adapted reduction in energy intakes [9]. Because exercise is the cornerstone of the countermeasure program to prevent unloading-induced loss of skeletal muscle mass and strength, bone, aerobic capacity and other health-related outcomes [14, 15], these observations suggest that understanding its role in energy balance regulation is critical, notably for long-duration missions.

This exploratory study was therefore designed to measure total energy expenditure (TEE) and activity energy expenditure (AEE), using the gold standard DLW method, in relation to body composition in 11 astronauts after at least 3 months onboard the ISS. Inferences to evaluate energy requirements in space were derived. We hypothesized that astronauts' individual BM and body composition changes are explained by inflight AEE.

2 Materials and Methods

Protocols, methodological validation and related assumptions of the calculations used are fully described in the Online Supplementary Material (OSM).

2.1 Participants

Eighteen astronauts (16 men and two women) voluntarily took part in the study between 2011 and 2017. All were subjected to extensive physical and medical examination prior to the flight. None had a history of chronic disease, and all of them were healthy throughout the mission. Out of the 18 astronauts, three (two men and one woman) performed preflight measurements only, due to rescheduling priorities during the flight, and four (three men and one woman) served as controls to correct for background isotopic changes on the ISS during an experimental session (see OSM Methods and OSM Figs. 1–3). Data presented here were therefore collected in 11 men.

The study was yearly approved by the NASA Institutional Review Board (IRB) under NASA 7116301606HR. European Space Agency (ESA) Medical Board and Japanese Space Agency (JAXA) IRB for human experiments also approved the protocol. Written informed consent was obtained from all astronauts.

2.2 Protocol

For the 11 remaining astronauts, each completed two research sessions of 10 days, one on Earth (ground) and one onboard the ISS (flight). The ground session was conducted within the year before flying, while astronauts were at the European Astronaut Center (EAC) in Cologne, Germany. On average, the mean delay between ground measurements and the flight was 99 days (standard deviation (SD) 78). The astronauts were deemed in energy balance the year before launch (see Fig. 1a and OSM Methods). The flight session was conducted after at least 3 months in space and before the last month onboard the ISS. This 3- to 5-month window was selected to provide data for long-term spaceflights while avoiding stress associated with the preparation for return to Earth. On average, flight sessions were conducted after 108 days (SD 19) in space.

Ground and flight experiments, strictly similar, were realized under the supervision of ESA and French Space Agency (CNES) science officers in charge of the experiment and the investigators from Toulouse Space Center (CADMOS, France), and were preceded by dry runs of the experiments conducted at EAC. BM and body composition, TEE and its components (resting metabolic rate (RMR) and AEE) and physical activity (PA) were measured. Additionally, postflight BM and composition were measured on the ground after landing.

2.3 Total Energy Expenditure and its Components

TEE was measured over 10 days using the doubly-labeled water (DLW) method as previously described [16]. The DLW is the gold standard to assess TEE in free living conditions. The technique is fully described in OSM Methods. Briefly, it is based on the exponential elimination of the stable isotopes ^{2}H and ^{18}O after a bolus dose of water labeled with both isotopes. The ^{2}H are lost as water, whereas the ^{18}O are lost both as water and as CO_2. Thus, the excess disappearance rate of ^{18}O relative to ^{2}H is a measure of the CO_2 production rate. This latter is converted to TEE using the food quotient or the respiratory quotient and the classic indirect calorimetry equations. On the DLW dosing day, RMR was measured in fasting state, at rest for 45 min using the Pulmonary Function System (PFS, manufactured by the Danish Aerospace Company, former DAMEC) [17]. AEE was calculated from TEE and RMR assuming a diet-induced thermogenesis of 10% of TEE. PA level (PAL) was calculated as the ratio between TEE and RMR.

2.4 Body Composition

Pre- and post-flight ground BM measures were obtained during NASA medical operations with a calibrated scale at EAC, and fat-free mass (FFM) and FM by dual X-ray energy absorptiometry (DXA, Hologic, Marlborough, MA, USA; software version 12.7.3.1 in 2011 to 15.5.3 in 2016). Inflight BM was measured using the SLAMMD (Space Linear Acceleration Mass Measurement Device) within 1 day of the DLW dosing day, and FFM and FM were obtained from the DLW method. BM, FFM and FM indexes (BMI, FFMI, FMI), were calculated by dividing BM, FFM and FM (in kg) by squared height (in squared m).

2.5 Energy Intake

Inflight mean daily EI, expressed in MJ/day, was calculated from the changes in body composition and TEE between the preflight and inflight DLW sessions deeming astronauts were in stable energy balance on ground measurements [18], and compared with theoretical EI calculated from the 2001 Dietary Reference Intakes (DRI) [19]. Details are provided in the OSM.

2.6 Physical Exercise and Activities

Physical training sessions were composed of both aerobic and resistive exercises and prescribed 6 days/week, as detailed in OSM Methods. Briefly, 30–45 min of aerobic exercise per session were prescribed on the cycle ergometer (CEVIS) or on a treadmill (T2) with vibration isolation system (OSM Fig. 4) [20, 21]. During treadmill exercise, an external vertical load (60–100% of BM) was applied to the astronauts to partially compensate for the absence of body weight in microgravity environment. The resistance exercise program consisted of three to three workouts per session that

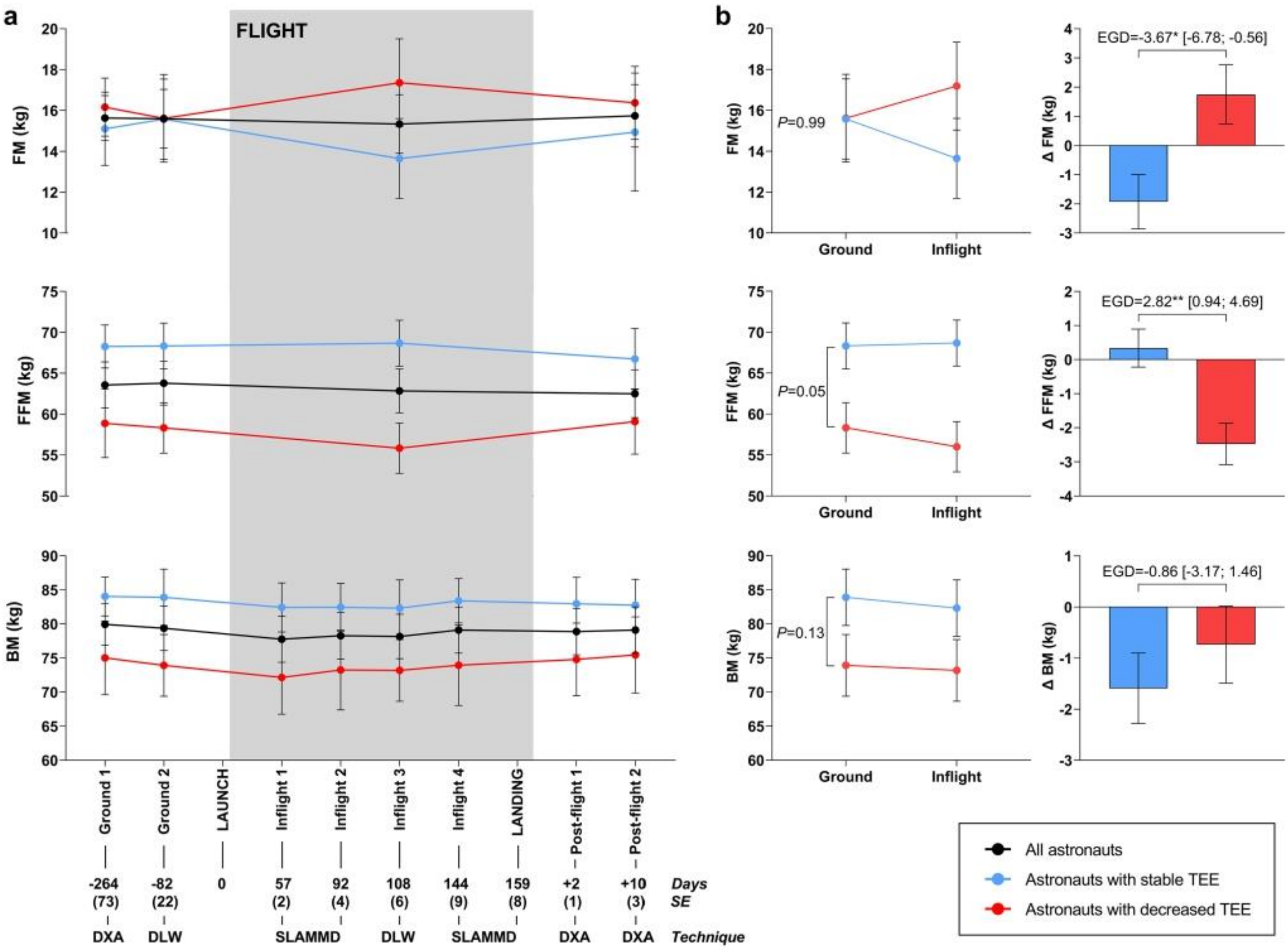


Fig. 1 Body mass and composition changes during flight. Changes in body mass and composition throughout the whole mission (**a**) and during the experimental sessions (**b**). Values are means (SE) (**a**), and lsmeans (SE) (**b**) from mixed-effects models for repeated measurements with estimated group differences (EGD) presented with their 95% confidence interval; $*P<0.05$; $**P<0.01$. *BM* body mass, *FFM* fat-free mass, *FM* fat mass, *DXA* dual X-ray absorptiometry, *SLAMMD* Space Linear Acceleration Mass Measurement Device, *DLW* doubly-labeled water

were performed on the advanced resistive exercise device (ARED) (OSM Fig. 4). Each workout was composed of five to seven exercises primarily focused on the lower body using 8–15 repetitions for 3–4 sets. Loads were individually adapted by the personal exercise trainers throughout the flight. Parameters of the exercise training actually performed during the spaceflight were obtained from the exercise dairy logs. Overall PA was further evaluated from a Sensewear Pro (SWP) activity monitor (Body media Inc®, Pittsburgh, PA, USA).

Self-reported exercise logs were provided by NASA. These logs included date and duration of each aerobic exercise session, the average speed and external load for T2, and average power and revolution per minute for CEVIS. For ARED, they included date and detailed exercise workouts of each resistive exercise session, with number of sets and repetitions, and loads. Mean daily and weekly exercise parameters were calculated over a period beginning 2 months before the experimental flight session (details in OSM files). An estimation of T2 power was derived from speed and external load from the American College of Sports Medicine (ACSM) formulas [22], and aerobic exercise workloads were calculated as power*duration. Resistive exercise workloads were calculated as sets*repetitions*loads [23]. Because the duration for the resistive exercise sessions was not provided, muscular time under tension was estimated from the number of repetitions, assuming a 2- to 5-s count for each repetition (i.e., including both concentric and eccentric phases), according to movement complexity from online video featuring this kind of exercise [24]. An additional 1-min resting time by set was added to approximate time involved with exercise on ARED. The goal of this calculation was to allow a comparison with the SWP-derived data.

The SWP, an activity multi-sensor armband that includes a bi-axial accelerometer, was worn on the non-dominant arm throughout the two 10-day DLW sessions. Its companion software (professional version 8.0) incorporates a proprietary machine-learning activity classification algorithm based on heat flux, galvanic skin response, skin and near-body ambient temperature and accelerometry measures patterns [25]. It was used to identify non-wear periods and, after exclusion of non-valid days, to obtain steps and categorize each minute in four classes: inactivity, walking, running and all other detected activities groups as non-ambulatory PA. Inflight valid data were obtained for nine astronauts only. The norm of the 1-min acceleration signal mean amplitude deviation (MAD) was used as an additional proxy of PA workload and intensity [26]. MAD removes the static component due to gravity from the acceleration signal to keep only the dynamic component due to body movements and changes in velocity. It is therefore poorly influenced by microgravity. Aggregation of 1-min MAD during activities, a composite variable that corresponds to the product of duration by the intensity of a given effort/exercise bout or of overall daily PA, are presented in milli-g (i.e., 0.001 g). Vigorous PA (VPA) was estimated using a MAD-cutpoint of 16 milli-g/min. Details are provided in OSM Methods.

2.7 Statistical Analyses

Data were first analyzed for the entire group of astronauts ($n=11$). To understand the inter-individual variability, astronauts were then stratified according to inflight TEE, i.e., either maintained close to preflight values (stable_TEE; $n=6$) or decreased (decreased_TEE; $n=5$).

Differences between the two groups stratified for inflight TEE changes at baseline and for inflight physical training were examined using unpaired Student's t tests. Linear mixed-effects models accounting for repeated measurements, with subjects as random effect and indicator for flight as fixed factor, were used to test the overall effect of spaceflight on the anthropometric, energetic and PA outcomes. The group effect (stable_TEE vs. decreased_TEE) on the flight-induced changes was tested by adding a group × flight interaction term. Our statistical inference was respectively on the overall outcome net changes and their between-group differences estimated (EGD) with their 95% confidence interval (CI). Effect size was estimated using Hedges'g, calculated as the EGD divided by the estimation of the groups' weighted pooled standard deviation, with a Hedges'g greater than 0.2, 0.5 and 0.8 indicating small, medium and large effect size, respectively [27]. TEE, AEE, EI and EB were further adjusted for mean BM, and RMR for both mean FM and mean FFM (whole group mean baseline values were used as reference values).

General linear models were used to examine the associations of (1) FFMI and FMI changes (inflight-preflight) with TEE and AEE changes (inflight-preflight), and (2) inflight FFMI and FMI with different inflight PA variables.

Baseline values and inflight physical training variables are presented as means (SD). Unless otherwise noted, results of the linear mixed-models are presented as least square means (standard error, SE). Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) with a significance level at 5%. Figures were realized with Prism 9 (GraphPad, San Diego, CA, USA).

3 Results

3.1 Few Spaceflight Changes for the Whole Group of Astronauts

At baseline (Table 1) astronauts had a mean age of 45.7 years (SD 7.7), a BMI of 24.3 kg/m^2 (2.1) with a normal-to-high FFMI of 19.6 kg/m^2 (1.9). They were quite active, as indicated by a TEE of 13.2 MJ/day (1.9), an AEE of 4.9 MJ/day (1.1) and a PAL of 1.90 (0.20). SWP-derived daily overall PA time was 161.8 min/day (56.3). This included 66.8 min/day (34.1) walking and 8.1 min/day (10.5) running, corresponding to a total of 10,077 steps/day (2834) and 7.4 min/day (9.2) of SWP-derived VPA.

Figure 1a presents the changes in BM and composition throughout the whole mission and Table 2 details the effect of at least 3 months in space on the main outcomes. Astronauts were in energy balance the year before launch and spaceflight had a modest impact on BM, FM and FFM. Compared to preflight values, BM decreased by 1.20 kg (SE 0.50; $P=0.04$) mainly due to a non-significant reduction in FFM of 0.94 kg (0.59; $P=0.14$).

No significant overall changes in TEE, RMR and AEE were noted between preflight and inflight (Table 2). However, inflight SWP-derived ambulatory activities dramatically dropped with daily steps decreasing by 6,583 steps/day (SE 730; $P<0.001$) and walking time by 63.2 min/day (SE 11.5; $P<0.001$). While SWP-derived running time remained stable at 14.4 min/day (SD 6.4), in agreement with the 13.3 min/day (SD 4.6) of self-reported time spent exercising on the T2, this reduction in ambulatory activities was almost fully compensated by an increase in SWP-derived non-ambulatory activities of 64.8 min/day (SE 18.8; $P<0.01$). This explained the absence of significant net changes in SWP-derived overall active time and accelerometry MAD, a proxy of overall PA workload. Daily SWP-derived VPA was not significantly different from ground values. The 1-h increase in non-ambulatory activities, leading to a total of 151.8 min/day (SE 18.9; range 119.7–194.5), was only partially explained by the

Table 1 Astronauts' baseline characteristics for the whole group and by inflight-total energy expenditure (TEE)-changes groups

	All astronauts ($n = 11$)	Astronauts with stable TEE ($n = 6$)	Astronauts with decreased TEE ($n = 5$)	Group difference *P* value[b]
Age and anthropometry				
Age (years)	45.7 (7.7)	43.5 (8.7)	48.4 (6.0)	0.32
Height (cm)	180.3 (6.7)	182.0 (5.7)	178.3 (7.9)	0.39
BM (kg)	79.4 (10.6)	83.9 (8.0)	73.9 (11.6)	0.13
BMI (kg/m^2)	24.3 (2.1)	25.3 (1.4)	23.2 (2.4)	0.10
FFM (kg)	63.8 (8.8)	68.3 (6.0)	58.3 (8.9)	0.05
FFMI (kg/m^2)	19.6 (1.9)	20.6 (1.5)	18.3 (1.6)	0.03
FM (kg)	15.6 (3.9)	15.57 (4.5)	15.6 (3.5)	0.99
FMI (kg/m^2)	4.8 (1.0)	4.7 (1.2)	4.9 (1.0)	0.71
Energetics				
TEE (MJ/day)	13.2 (1.9)	14.0 (1.4)	12.2 (2.1)	0.13
TEE_{BM} (MJ/day)[a]	13.2 (1.0)	13.3 (1.2)	13.0 (1.3)	0.70
RMR (MJ/day)	7.0 (1.2)	7.4 (1.4)	6.6 (0.8)	0.32
$\text{RMR}_{\text{FFM \& FM}}$ (MJ/day)[a]	7.0 (1.0)	7.0 (1.3)	7.0 (1.4)	0.93
AEE (MJ/day)	4.9 (1.1)	5.2 (1.0)	4.4 (1.1)	0.24
AEE_{BM} (MJ/day)[a]	4.9 (0.9)	5.0 (1.1)	4.7 (1.1)	0.71
PAL	1.90 (0.20)	1.94 (0.26)	1.85 (0.09)	0.50
Energy intake (MJ/day)	13.2 (1.9)	14.0 (1.4)	12.2 (2.1)	0.13
Energy $\text{intake}_{\text{BM}}$ (MJ/day)[a]	13.2 (1.1)	13.3 (1.2)	13.0 (1.3)	0.70
SWP-derived physical activities				
Steps (number/day)	10,077 (2834)	1046 (2816)	9614 (3111)	0.65
Overall activity and exercise (min/day)	161.8 (56.3)	164.8 (67.5)	158.3 (47.0)	0.86
Walking (min/day)	66.8 (34.1)	60.2 (27.1)	74.6 (43.1)	0.53
Running (min/day)	8.1 (10.5)	13.7 (11.5)	1.5 (2.8)	0.04
Non-ambulatory activity and exercise (min/day)	87.9 (63.4)	90.9 (61.7)	82.3 (72.4)	0.84
Vigorous physical activity (MAD > 16 milli-g; min/day)	7.4 (9.2)	12.4 (9.8)	1.3 (2.6)	0.04
Accelerometry MAD				
Daily total (milli-g/day)	1353 (278)	1487 (309)	1193 (124)	0.08
Overall activity and exercise (milli-g/day)	692 (313)	814 (368)	546 (164)	0.17
Walking (milli-g/day)	286 (171)	250 (104)	329 (235)	0.47
Running (milli-g/day)	188 (242)	322 (259)	27 (54)	0.04
Non-ambulatory activity and exercise (milli-g/day)	218 (141)	241 (151)	190 (140)	0.58
Overall activity and exercise mean intensity (milli-g/min)	4.3 (1.1)	4.9 (0.9)	3.5 (0.9)	0.03

Values are means (SD)

Physical activities were derived from a combination of different physiological signals with an in-built machine-learning activity classification algorithm

BMI body mass index, *FM* fat mass, *FFM* fat-free mass, *FMI* fat mass index, *FFMI* fat-free mass index, *TEE* total energy expenditure, *RMR* resting metabolism rate, *AEE* activity energy expenditure, *EI* energy intake, *MAD* acceleration mean absolute deviation, *SWP* Sensewear Pro activity-device

[a] BM (TEE, AEE, EI) or FFM and FM (RMR) adjusted lsmeans (SD) (whole group mean baseline values were used as reference values). All astronauts were male

[b] Statistical analyses used Student's *t* tests

10.7 min/day (SD 4.4) spent on the CEVIS and the about 29.0 min/day (SD 14.3) on the ARED as reported by the astronauts (OSM Table 1). This suggested an increase in PA not related to physical training. Overall, the astronauts reported 6.2 aerobic exercise sessions/week (SD 1.4; range 3.6–8.6) corresponding to a total duration of 167.8 min/week (SD 43.9; range 86.9–257.8). They reported 4.5 resistance training sessions/week (SD 1.8; range 1.8–6.6), consisting of 5.9–10.2 exercises using 8.8–15.1 repetitions for 2.2–3.2 sets. This led to a total of 1481 repetitions/week (SD 834;

Table 2 Astronauts' anthropometric, energetic and physical activity changes between preflight and flight for the whole group and by inflight-total energy expenditure (TEE)-changes groups

	All astronauts ($n=11$)		Astronauts with stable TEE ($n=6$)	Astronauts with decreased TEE ($n=5$)	Linear mixed model analyses		
	Changes from preflight	*P* value	Changes from preflight	Changes from preflight	EGD in changes from preflight	95% CI	*P* value
Age and anthropometry							
BM (kg)	− 1.20 (0.50)	0.04	− 1.59 (0.69)	− 0.74 (0.75)	− 0.86 (1.02)	− 3.17 to 1.46	0.42
BMI (kg/m^2)	− 0.39 (0.17)	0.04	− 0.49 (0.24)	− 0.28 (0.26)	− 0.22 (0.35)	− 1.01 to 0.57	0.55
FFM (kg)	− 0.94 (0.59)	0.14	0.34 (0.56)	− 2.48 (0.61)	2.82 (0.83)	0.94 to 4.69	<0.01
FFM index (kg/m^2)	− 0.29 (0.18)	0.13	0.10 (0.16)	− 0.76 (0.18)	0.87 (0.24)	0.32 to 1.41	<0.01
FM (kg)	− 0.26 (0.87)	0.77	− 1.93 (0.93)	1.74 (1.02)	− 3.67 (1.38)	− 6.78 to − 0.56	0.03
FM index (kg/m^2)	− 0.11 (0.27)	0.70	− 0.60 (0.29)	0.49 (0.32)	− 1.09 (0.43)	− 2.06 to − 0.11	0.03
Energetics							
TEE_{BM} (MJ/day)[a]	− 0.39 (0.73)	0.60	0.90 (0.37)	− 2.08 (0.40)	2.98 (0.54)	1.75 to 4.22	<0.001
$\text{RMR}_{\text{FFM \& FM}}$ (MJ/day)[a]	− 0.15 (0.19)	0.43	− 0.35 (0.28)	0.11 (0.33)	− 0.46 (0.48)	− 1.51 to 0.59	0.36
AEE_{BM} (MJ/day)[a]	− 0.19 (0.70)	0.79	1.12 (0.36)	− 1.90 (0.39)	3.02 (0.53)	1.81 to 4.23	<0.001
PAL	− 0.02 (0.10)	0.86	0.23 (0.08)	− 0.31 (0.09)	0.54 (0.12)	0.28 to 0.80	0.001
Energy intake (MJ/day)	− 0.82 (0.38)	0.06	0.06 (0.34)	− 1.86 (0.37)	1.92 (0.50)	0.78 to 3.05	<0.01
Energy $\text{intake}_{\text{BM}}$ (MJ/day)[a]	− 0.61 (0.40)	0.16	0.29 (0.33)	− 1.75 (0.36)	2.04 (0.48)	0.96 to 3.13	<0.01
Energy balance (MJ/day)	− 0.15 (0.29)	0.61	− 0.68 (0.33)	0.48 (0.36)	− 1.15 (0.49)	− 2.19 to − 0.12	0.03
Energy $\text{balance}_{\text{BM}}$ (MJ/day)[a]	− 0.14 (0.30)	0.65	− 0.63 (0.30)	0.50 (0.33)	− 1.13 (0.44)	− 2.06 to − 0.20	0.02
SWP-derived physical activities							
Steps (number/day)	− 6583 (730)	<0.001	− 6277 (1402)	− 7231 (1554)	954 (2093)	− 3483 to 5391	0.66
Overall activity and exercise (min/day)	13.2 (23.8)	0.59	24.4 (33.2)	− 0.9 (36.8)	25.2 (49.6)	− 79.9 to 130.3	0.62
Walking (min/day)	− 63.2 (11.5)	<0.001	− 57.3 (16.0)	− 70.1 (17.7)	12.8 (23.9)	− 37.8 to 63.4	0.60
Running (min/day)	6.3 (4.0)	0.13	4.4 (4.5)	8.5 (5.0)	− 4.1 (6.7)	− 18.3 to 10.1	0.55
Non-ambulatory activity and exercise (min/day)	64.8 (18.8)	<0.01	77.3 (36.3)	60.8 (40.2)	16.5 (54.2)	− 98.3 to 131.4	0.76
Vigorous physical activity (MAD > 16 milli-g; min/day)	2.8 (2.1)	0.23	4.3 (4.2)	3.3 (4.6)	1.0 (6.2)	− 12.2 to 14.1	0.88
Accelerometry MAD							
Daily total (milli-g/day)	− 40.8 (74.7)	0.60	12.6 (147.3)	− 67.9 (163.1)	80.5 (219.8)	− 385.4 to 546.4	0.72
Overall activity and exercise (milli-g/day)	11.1 (93.2)	0.91	70.2 (169.0)	− 40.4 (187.2)	110.7 (252.2)	− 424.0 to 645.4	0.67
Walking (milli-g/day)	− 264.6 (57.3)	<0.001	− 235.0 (79.4)	− 299.9 (87.9)	64.9 (118.5)	− 186.2 to 316.1	0.59
Running (milli-g/day)	113.2 (73.8)	0.16	138.4 (118.3)	127.5 (131.1)	10.9 (176.6)	− 363.4 to 385.3	0.95
Non-ambulatory activity and exercise (milli-g/day)	151.8 (60.9)	0.02	166.8 (83.8)	132.0 (92.9)	34.8 (125.1)	− 230.4 to 300.0	0.78

Table 2 (continued)

	All astronauts ($n = 11$)		Astronauts with stable TEE ($n = 6$)	Astronauts with decreased TEE ($n = 5$)	Linear mixed model analyses		
	Changes from preflight	P value	Changes from preflight	Changes from preflight	EGD in changes from preflight	95% CI	P value
Overall activity and exercise mean intensity (milli-g/min)	− 0.23 (0.35)	0.53	− 0.32 (0.55)	− 0.16 (0.61)	− 0.16 (0.82)	− 1.90 to 1.58	0.84
Activity NASA logs^{c}							
T2 (min/day)	13.3 (1.4)		15.7 (1.6)	10.4 (1.7)	− 5.3 (2.3)	− 10.5 to − 0.1	0.04
CEVIS (min/day)	10.7 (1.3)		10.0 (1.9)	11.4 (2.1)	1.4 (2.8)	− 4.9 to 7.7	0.63
ARED (min/day)^{d}	29.0 (4.3)		30.9 (6.1)	26.8 (6.7)	− 4.1 (9.0)	− 24.5 to 16.4	0.66

Physical activities were derived from a combination of different physiological signals with an in-built machine-learning activity classification algorithm

BMI body mass index, *FM* fat mass, *FFM* fat-free mass, *FMI* fat mass index, *FFMI* fat-free mass index, *TEE* total energy expenditure, *RMR* resting metabolism rate, *AEE* activity energy expenditure, *EI* energy intake, *EB* energy balance, *MAD* acceleration mean absolute deviation, *T2* treadmill device onboard the ISS, *CEVIS* Cycle Ergometer with Vibration Isolation and Stabilization system, *ARED* Advanced Resistive Exercise Device, *SWP* Sensewear Pro device

Values are estimated Lsmeans (SE) from a mixed-effects models for repeated measurements

[a] BM (TEE, AEE, EI, EB) or FFM and FM (RMR) adjusted models (whole group mean baseline values were used as reference values)

[c] Inflight values

[d] ARED duration was approximate from number of repetitions and sets (2-to5 sec/repetition, according to movement complexity, with addition of 1-min recuperation time by set)

range 468–3,044) and a muscular time under tension of 81.8 min/week (SD 43.5; range 28.8–161.2). These numbers exhibit a great inter-individual variability in the adherence to the exercise prescriptions. They are to be compared to the 180–270 min/week aerobic, and six resistive exercise sessions/week (corresponding to about 1500 repetitions/week) recommendations [21].

The astronauts were stratified into two groups, according to their inflight TEE changes, i.e., no change in TEE or decrease in TEE compared to preflight values. Fortuitously, the two groups ended up having an almost equal number of subjects.

3.2 Baseline Characteristics of Inflight-Total Energy Expenditure (TEE)-Changes Groups

At baseline (Table 1), both groups were of the same age and had similar FMI but, compared to the decreased_TEE group, the stable_TEE astronauts had higher FFMI (20.6 kg/m^2 [SD 1.5] vs. 18.3 kg/m^2 [1.6]; $P = 0.03$) and presented a more active profile. TEE, AEE and daily SWP-derived overall active time did not differ between the two groups. However, the stable_TEE astronauts spent more time on ground in SWP-derived VPA (12.4 min/day [9.8] vs. 1.3 min/day [2.6]; $P = 0.04$) and running ($P = 0.04$), and had higher running-related MAD ($P = 0.04$) resulting in greater SWP-derived mean activity intensity (4.9 milli-g/min [0.9] vs. 3.5 milli-g/min [0.9]; $P = 0.03$) than the decreased_TEE astronauts.

3.3 Anthropometric Changes by Inflight-TEE-Changes Groups

Compared to preflight, both groups lost equivalent BM, but contrasted changes in body composition were noted (Table 2 and Fig. 1a, b). While the stable_TEE group maintained FFMI and displayed a slight FMI loss, their counterparts lost FFMI and gained FMI. The EGD for FFMI changes (stable_TEE compared to decreased_TEE group) was + 0.87 kg/m^2 (95% CI 0.32–1.41; effect size = 1.7; $P < 0.01$); and the EGD for FMI changes − 1.09 kg/m^2 (95% CI -2.06 – -0.11; effect size = 1.2; $P = 0.03$).

3.4 Energy Expenditure Changes by Inflight-TEE-Changes Groups

The EGD for TEE changes adjusted for BM was + 2.98 MJ/day (95% CI 1.75–4.22; effect size = 2.6; $P < 0.001$), mainly related to differences in AEE changes (BM-adjusted EGD + 3.02 MJ/day, 95% CI 1.81–4.23; effect size = 2.7; $P < 0.001$) while RMR remained stable in both groups (Table 2 and Fig. 2a). As illustrated in Fig. 2b, the individual FMI net changes were negatively associated with net changes in TEE ($R^2 = 0.58$; $P < 0.01$) and AEE ($R^2 = 0.54$; $P = 0.01$) while net changes in FFMI were positively associated with net changes in TEE ($R^2 = 0.64$; $P < 0.01$) and, to a lesser degree, net changes in AEE ($R^2 = 0.47$; $P = 0.02$).

3.5 Physical Activity Changes by Inflight-TEE-Changes Groups

Net changes in SWP and accelerometry-derived activity parameters (Table 2 and Fig. 3a) were globally similar across groups. However, as what was observed on the ground, the stable_TEE astronauts still spent more time inflight in SWP-derived VPA (16.7 min/day [SE 3.1] vs. 4.6 min/day [3.4]; $P = 0.02$), had higher overall-activity accelerometry MAD (884 milli-g/day [125] vs. 505 milli-g/day [140]; $P = 0.06$), and SWP-derived mean activity intensity (4.60 milli-g/min [0.41] vs. 3.35 milli-g/min [0.45]; $P = 0.06$) than the decreased_TEE group. Reported inflight resistance training characteristics and time spent performing CEVIS were not significantly different between groups (OSM Table 1). The stable_TEE group reported non-significant higher inflight aerobic workloads than the decreased_TEE group ($P = 0.10$), due to more time spent on T2 (15.7 min/day [SD 3.0] vs. 10.4 min/day [4.6]; $P = 0.05$) but also to higher average speeds (11.2 [0.9] vs. 8.5 [2.1] km/h; $P = 0.02$). This was in good agreement with higher SWP-derived running-times (18.0 min/day [SE 3.3] vs. 9.9 min/day [3.7]; $P = 0.12$) and running-related accelerometry MAD (461 milli-g/day [SE 87] vs. 154 milli-g/day [98]; $P = 0.03$).

As illustrated in Fig. 3b, after at least 3 months on the ISS, individuals' inflight FMI were inversely associated with SWP-derived overall activity-related accelerometry MAD ($R^2 = 0.73$; $P < 0.01$), time spent in SWP-derived VPA ($R^2 = 0.56$; $P = 0.02$), and self-reported T2 relative workload ($R^2 = 0.71$; $P = 0.001$). Conversely FFMI values were positively associated with SWP-derived overall activity-related accelerometry MAD ($R^2 = 0.48$; $P = 0.04$), time spent in SWP-derived VPA ($R^2 = 0.62$; $P = 0.01$) and self-reported T2 relative workload ($R^2 = 0.40$; $P = 0.04$). Practice of ARED and CEVIS was not associated with any body composition parameter.

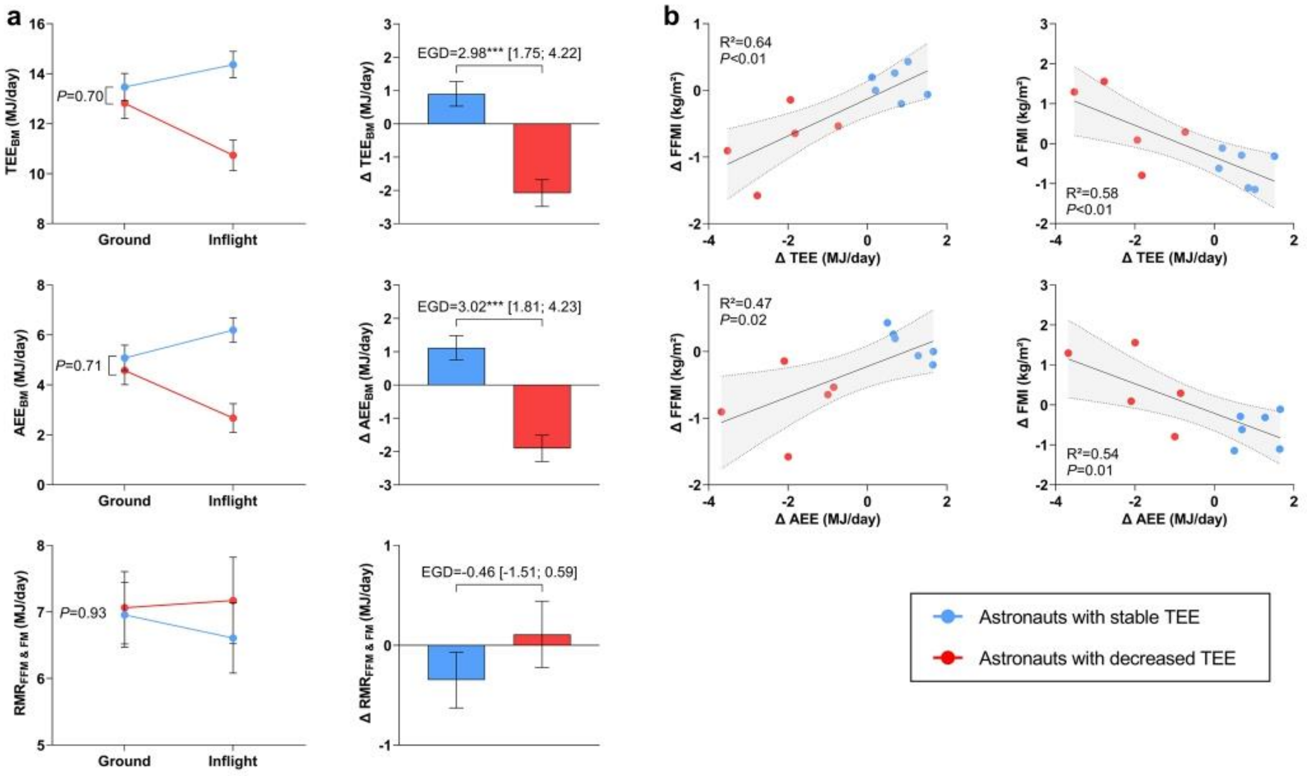
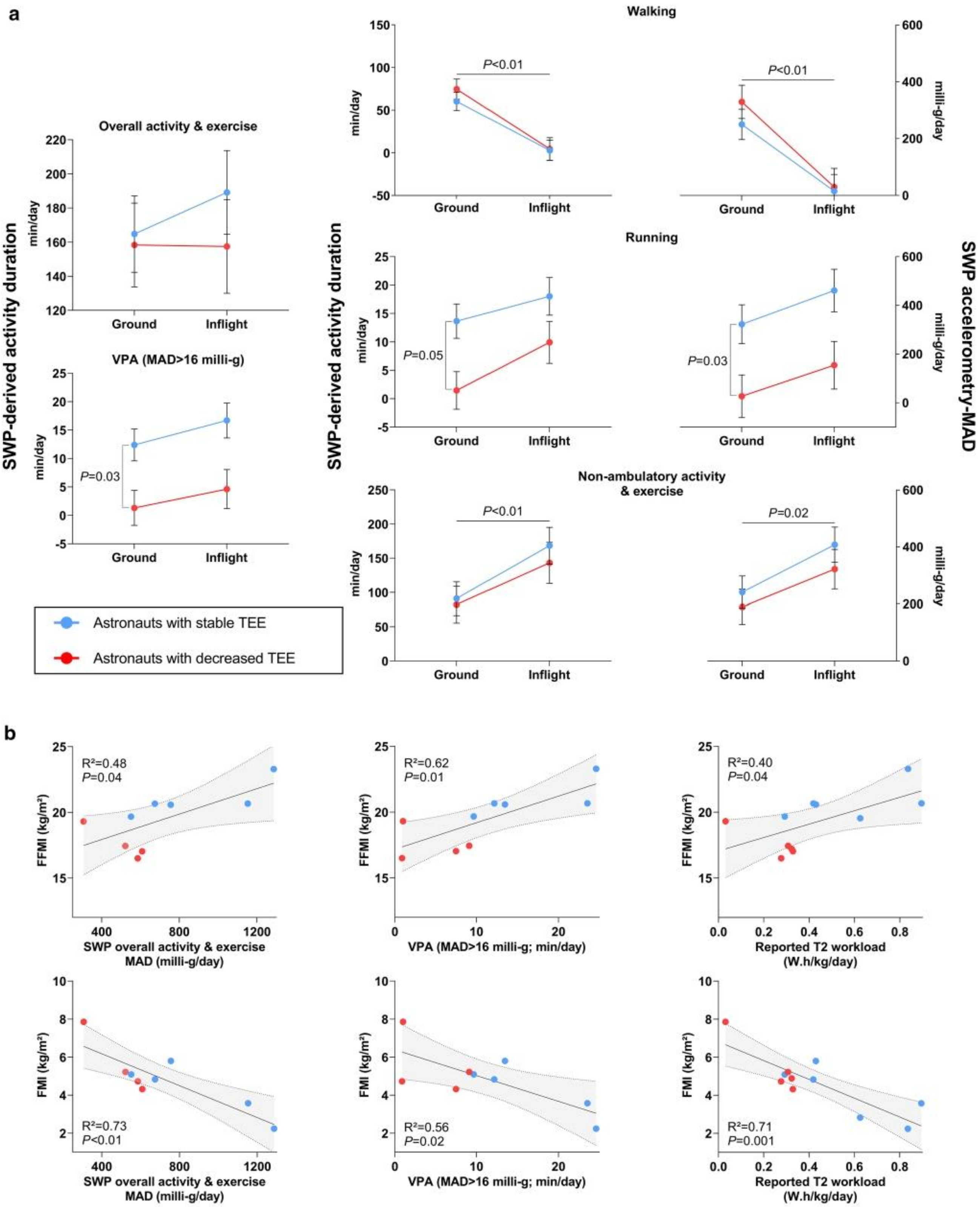


Fig. 2 Energy expenditure changes during flight. Changes in total energy expenditure and its components during the experimental sessions (**a**) and scatterplots for the relationship between body composition changes and energy expenditure components changes (**b**). Values are lsmeans (SE) from mixed-effects models for repeated measurements with estimated group differences (EGD) presented with their 95% confidence interval; ***$P < 0.001$ (**a**). Least square regression lines are plotted with their 95% confidence interval in shaded areas (**b**). TEE_{BM} total energy expenditure adjusted for body mass, AEE_{BM} activity-related energy expenditure adjusted for body mass, $RMR_{FFM\ \&\ FM}$ resting metabolic rate adjusted for fat-free mass and fat mass, *FFMI* fat-free mass index, *FMI* fat mass index


a
SWP-derived activity duration
Overall activity & exercise
min/day
Ground
Inflight
VPA (MAD>16 milli-g)
P=0.03
Astronauts with stable TEE
Astronauts with decreased TEE
Walking
P<0.01
P<0.01
milli-g/day
Running
P=0.05
P=0.03
SWP accelerometry-MAD
Non-ambulatory activity & exercise
P<0.01
P=0.02
b
FFMI (kg/m²)
FMI (kg/m²)
R²=0.48
P=0.04
R²=0.62
P=0.01
R²=0.40
P=0.04
R²=0.73
P<0.01
R²=0.56
P=0.02
R²=0.71
P=0.001
SWP overall activity & exercise MAD (milli-g/day)
VPA (MAD>16 milli-g; min/day)
Reported T2 workload (W.h/kg/day)

◂**Fig. 3** Physical activity changes during flight. Changes in SWP-derived activity duration and acceleration-MAD (as a proxy of activity workload) during the experimental sessions (**a**) and scatterplots for the relationship between inflight body composition and inflight SWP-derived or reported physical activity (**b**). Values are lsmeans (SE) from mixed-effects models for repeated measurements (**a**). Least square regression lines are plotted with their 95% confidence interval in shaded areas; individual values are available for nine astronauts only (**b**). *FFMI* fat-free mass index, *FMI* fat mass index, *T2* treadmill device onboard the International Space Station, *SWP* Sensewear Pro activity monitor, *MAD* acceleration mean amplitude deviation, *VPA* vigorous physical activity (MAD > 16 milli-g)

3.6 Energy Intakes by Inflight-TEE-Changes Groups

EI (BM-adjusted) calculated from changes in body composition from the time of beginning of spaceflight to the time of starting the inflight TEE measurement was 13.6 MJ/day (SE 0.5) in the stable_TEE group and 11.3 MJ/day (0.6) in the decreased_TEE group, representing 93% and 75% of DRIs, respectively (Fig. 4).

4 Discussion

The aim of the ENERGY study was to assess the regulation of energy balance and body composition during 6- month missions onboard the ISS by specifically considering the energy cost of PA using the gold standard DLW method. Despite no significant overall changes in body composition and energy expenditures, a slight decrease in BM (-1.5%) was observed in the whole group of astronauts. A large interindividual variability was, however, noticed. Astronauts who maintained pre-flight total and activity energy expenditures kept fat-free mass at baseline levels but lost fat mass. Conversely, those who expended less energy during the flight than on the ground lost fat-free mass and gained fat mass. Astronauts who maintained stable TEE during the flight spent more time inflight running and engaged in VPA, and were also the ones with the best fitness on the ground. These results suggest that (1) inflight AEE, possibly due to both physical training and non-exercise PA, drives inflight body composition regulation; (2) inflight energy requirements should be individually evaluated during the whole duration of the spaceflight; (3) baseline participants' characteristics need to be considered for the prescription of both preflight and inflight exercise training; and (4) fat mass changes result from unmatched spontaneous EI adaptation to changes in AEE in space that require further investigation.

4.1 Ground Fitness and Physical Acdtivity (PA) Performance Influence Changes in Body Composition During Spaceflight

After at least 3 months onboard the ISS, the 11 astronauts presented a slight BM loss, mainly due to a reduction in FFM, despite no significant changes in TEE. The modest effect of spaceflight on BM and body composition in the whole group masked a large interindividual variability with half of the group of astronauts who maintained a stable FFM favoring a slight BM loss (stable_TEE group), while the other half displayed a FFM loss but an increase in FM (decreased_TEE group). This between-subject variability seemed to be associated with heterogeneity in astronauts' ground body composition and engagement in exercise of high intensity [15]. Although all the astronauts were quite fit and active on the ground, those who maintained their FFM during the flight had higher FFMI and spent more time running or in VPA on Earth. These results are in line with the study of Matsumoto et al. [6] that showed habitual PA on Earth was a better predictor of inflight BM loss than PA performed during spaceflight. Whether habitual ground activity levels affect inflight body mass and composition directly or are due to greater engagement of fitter astronauts in exercise during the mission requires further investigations. Of interest, ground differences in SWP-derived VPA and running persisted during the flight with a significant reduction in inflight energy expenditures in the astronauts who were the least active on Earth, but not in the others. We also observed significant associations of inflight self-reported running or SWP and accelerometry proxies of PA workload and intensity with body composition. While improvement of exercise hardware capabilities and prescription have led to better post-flight performances, predicting appropriate inflight exercise loads remains difficult because of the difference in training environment (gravity vs. microgravity) and hardware [20, 21]. Beyond their energetics implications, our findings indicate that gaining a better understanding of the associations between ground and inflight exercise characteristics may help designing preflight and inflight prescriptions that favor adherence and enhance inflight performance including for the occupation-related astronaut tasks. Altogether these data suggest that pre-flight astronauts' individual anthropometric and fitness characteristics require more attention for onboard exercise prescriptions and EI recommendations.

4.2 Does the Exercise Countermeasure Play a Role in the Regulation of Body Composition?

The strong associations of TEE and AEE changes with FFMI and FMI changes suggest that activity-related energy expenditure, in interaction with microgravity exposure, plays a role in inflight body composition changes. In the absence of gravity, TEE is driven by the exercise countermeasure and intra- and extra-vehicular activities while energy expenditure related to standing posture and weight-bearing muscle activity is suppressed. For the first time, SWP and accelerometry used in this study gave a more detailed insight into onboard overall PA patterns. It clearly highlighted the

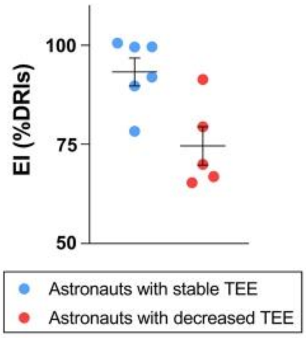


Fig. 4 Estimated energy intakes during flight. Percentage of energy intake (EI) estimated from the changes in body composition and total energy expenditure between the preflight and inflight experimental sessions from the 2001 Dietary Reference Intakes (DRIs) [19] for each groups stratified for inflight TEE changes. Values are individual data and means (SE)

expected decrease in ambulatory activities, except for running activity performed on the T2 treadmill. Contrary to our expectations, averaged overall PA time and workload, as estimated by SWP and accelerometry MAD, were not reduced on the ISS; the decrease in ambulatory activities was compensated by non-ambulatory activities. Of interest, accelerometry MAD removes from accelerometry signal any static gravitation component [26] and SWP utilizes the signature of several physiological systems (temperature, sweat, and heat flux and dissipation) in addition to accelerometry, which allows for the disambiguation of activities and contexts (e.g., microgravity) that may confuse a single sensor [25]. Inflight non-ambulatory activities (almost 2.5 h/day) can only be partially explained by the CEVIS and ARED exercises, which represent about 40 min/day altogether. This suggests that routine and off-nominal mission tasks may be another important component of overall PA. Unfortunately, the identification of specific onboard activities based on the SWP other than walking and running, was not possible due to the arm-placement of the device and the absence of activity learning studies in microgravitational conditions.

Mean self-reported training exercises were slightly lower than the recommendations. This was in agreement with previous observations made on the ISS [28]. The lower levels of aerobic exercise reflect a recent tendency to favor resistive exercise for its effect on muscle and bone mass and strength [29, 30]. More importantly, a large inter-individual variability in exercise adherence was observed with some astronauts reporting no more than 87 min/week of aerobic exercise and less than 500 repetitions/week in resistive exercise with a muscular time under tension lower than 30 min/week.

Even if efficiency is lower in space than on the ground, AEE does not seem to be fully explained by exercise training inflight. Treadmill exercise, characterized by higher weekly duration and speed in the astronauts who maintained their TEE, was undoubtedly a contributor of higher AEE and was inversely associated with astronauts' FM changes. Conversely both inflight SWP-derived VPA and T2 workload were positively associated with FFM confirming the protective role of exercise intensity on muscle mass [30]. Of note, time spent on the treadmill alone did not seem to explain the between-group differences in SWP-derived VPA. This suggests that VPA may also reflect an engagement in energy-demanding mission-related activities. However, any extrapolation from SWP sensors about the exact energy cost of both non-training and specific training activities in the context of spaceflights was not possible. Although resistive exercise is considered important to prevent muscle mass and bone loss, we surprisingly did not find any relationship between ARED practice and FFM.

4.3 Energy Intakes During Long-Term Spaceflight

Even if, by reviewing data from past space missions, no association was found between inflight unadjusted EI and BM loss [6], insufficient EI has often been reported during long-term missions [7, 13]. Astronauts in this study consumed about 85% of dietary prescriptions [19], which is similar to self-reported values observed by Smith et al.[7] during past missions onboard the ISS. Hyporexia due to lower food attractivity, altered smell or taste, sickness, or other microgravity-induced disorders [8] are expected to impair the spontaneous adjustment of EI to the changes in energy needs [7, 31]. This may explain why the astronauts who maintained their TEE to preflight values lost FM despite EI close to their theoretical energy requirements. Conversely, the reduction in EI observed in the less active astronauts was expected as their TEE was reduced by about 20%, due to a decrease in AEE. However, despite EI only representing 75% of the dietary recommendations, the astronauts who displayed a decrease in TEE during spaceflight were still in positive energy and fat balance.

4.4 How to Maintain Energy Balance During Long-Term Spaceflight?

Exercise countermeasure is the cornerstone of countermeasure programs during human spaceflights. Exercise training is known to benefit several physiological systems, including muscle strength, bone density and aerobic capacity, but effects of the exercise on these health outcomes were beyond the scope of this study. Here we showed that FFM was maintained in the stable_TEE astronauts despite some of them completing less than the prescribed exercise sessions. Our results further suggest that the non-ambulatory non-training activities play a role in the regulation of energy balance. The extent to which these activities, likely related to the occupational tasks on the ISS, influence energy expenditures and body composition remains to be addressed. For example, it is not known how it contributes to the preservation of muscle mass or other critical key performance outcomes. This finding has potential implications for future spaceflights as it calls for considering non-training activities and their associated energy cost when developing the exercise countermeasure [15], especially for long-term space missions.

This does not preclude the need for improving strategies to help astronauts to comply with the exercise prescriptions. Space agencies must find the best combination between modalities, i.e., duration and intensity for the aerobic exercise, and load and repetitions for the resistive exercise, to benefit most of the physiological systems without affecting others. For example, using high intermittent interval training (HIIT) that efficiently stimulates musculoskeletal and cardiovascular systems with a relatively low impact on energy requirements may be a promising alternative [8, 15, 23, 32]. Other countermeasure such as nutrition or artificial gravity may also be used to optimize the benefits of exercise and PA. In parallel, changes in the agenda of the astronauts could be considered to improve time dedicated to meals for the whole crew together, and food could be further improved to favor a better adjustment to actual energy needs [33, 34].

Overall, the results of this study show that both the measurement and regulation of energy balance inflight are challenging. One of the key findings is the large between-subject variability in changes in TEE, AEE and body composition. This variability was previously reported for EI. This has challenging consequences for both exercise and EI prescriptions as a complex tradeoff needs to be assessed. Such a tradeoff would need to consider both the positive impact on health and various physiological functions of high AEE along with adequate EI; but also the negative impact of too low AEE and excessive FM gain. This is why research on both exercise countermeasures and the development of loggers accurately assessing on real-time exercise, energy expenditure and body composition at the individual level is a top priority. Clearly current available devices (along with their algorithms) do not allow to do so and further interdisciplinary studies are needed.

4.5 Limitations and Strengths of the Study

Spaceflight imposes some limitations and strengths that need to be acknowledged. The sample size was relatively low, due to the limited number of inflight experiments. This study was conducted in male astronauts only, and results may not apply to women. Because spaceflights are limited, this study is one of the only three studies that determined energy requirements and body composition changes inflight using gold standard objective methods such as DLW and activity monitors, but it is the first one to focus on long-duration missions. Utilization of a unique combination of sensors for continuous physiological monitoring related to PA is a strength of the SWP device. As already underlined, the activity classification algorithms were, however, developed for detecting activities on Earth, limiting their current recognition capabilities and energy extrapolations in the context of spaceflights. Unfortunately, the R&D service of the SenseWearPro company no longer exists and the SWP software is no longer updated. The current version of the software only provides one-min aggregate measures rather than raw signals, which preludes any additional data treatment and validation. Also, heart rate monitoring, an additional valuable physiological signal in the context of exercise and energy evaluation, was available for few astronauts and during the training sessions only. On the other side, making assumptions on exercise performance based on crewmember exercise logs was challenging and not possible for non-training activities. Many of the findings are correlations, which suggests the need for future studies to prove causation.

5 Conclusion

The between-astronauts variability in body composition and energy expenditure changes observed during spaceflight was related to ground fitness, and inflight practice of activities of high intensity. Importantly, a high inter-individual variability in inflight training was noted with some crewmembers reporting values far below the recommendations, but there was an unexpected engagement in non-ambulatory activities related to the nature of the missions onboard the ISS. These results suggest that energy requirements in space must be individually derived based on real-time measurements of AEE and changes in body composition rather than on current general recommendations and exercise prescriptions. This requires validating in space the use of tri-axial accelerometry on different body parts, along with other sensors including heart rate monitors, and the development of specific algorithms to detect and quantify all physical activities and derive activity-specific energy expenditures during the space missions. Despite some spontaneous adjustments, we further observed an uncoupling between energy intakes and expenditures that led to energy imbalance. Methodological developments are therefore vital for the control of both sides of the energy balance, i.e., energy intakes and expenditures, or at least body composition evolution during long-duration space missions, which are considered a top priority for exploration by the international space agencies.

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Declarations

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Conflicts of interest PB, AZ, DSA, IC, ELR, CT, AM, MG, GGK, AB, CS and SB declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

Availability of data and material Data are accessible upon reasonable request to the authors after validations by space agencies.

Ethics approval The study was approved yearly by the NASA Institutional Review Board under NASA 7116301606HR. The ESA Medical Board and the JAXA Institutional Review Board for human experiment also approved the experiment.

Consent to participate The study was conducted in conformity with the policy statement regarding the use of human participants as outlined in the Declaration of Helsinki of 1964. All astronauts received a detailed presentation of the experiment before enrolling the study and signed a written informed consent.

Consent for publication A global authorization from the European Space Agency was obtained to use and publish the photos (ESA copyright).

Author contributions SB, DAS, GGK and AM designed the study. PB, AB, CS and SB drafted the manuscript. AZ, CT, AM, GGK, CS and SB collected data. PB, ELR, AZ, DAS, IC, MG, AB, CS and SB analyzed the data. CS and PB realized the statistical analysis. All the authors read and approved the final version of the manuscript.

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3. Supplementary information

Effect of exercise on energy expenditure and body composition in astronauts onboard the International Space Station: Considerations for interplanetary travel

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Material and Methods

Participants

Eighteen astronauts (16 men and 2 women) who flew for 6 months onboard the ISS between 2011 and 2017 voluntarily took part in the study. Astronauts came from eight countries: United States, Japan, Italia, Canada, France, Germany, United Kingdom and The Netherlands. All were subjected to extensive physical and medical examination annually and immediately before the flight. None had history of chronic disease, and all of them were healthy throughout the missions.

Out of the 18 astronauts, two performed only pre-flight measurements due to rescheduling priorities during the flight. Four astronauts served as controls to check the stability of isotopic enrichments of potable water on the ISS during an experimental session (**Supplemental figures 1 to 3**). Data on energy metabolism are therefore presented for 11 male astronauts.

The study was yearly approved by the NASA Institutional Review Board under the reference NASA 7116301606HR. The ESA Medical Board and the JAXA Institutional Review Board for human experiment also approved the experiment supervised by NASA. All astronauts had an individual detailed presentation of the experiment before signing a written informed consent.

Protocol

Each astronaut completed two research sessions of 10 days, one on Earth (ground) and one done onboard the ISS (inflight). The ground session was realized within the year before launching during a time slot when astronauts were at the European Astronaut Center (EAC) in Cologne, Germany. On average ground measurements were conducted 99 days (SD 78) before flight. Body mass (BM) and composition were measured either by dual X-ray absorptiometry (DXA) (NASA medical operations) or hydrometry (this current study) during the year before flight. The average within-subject coefficients of variation in body composition during this period were 1.7% for BM (n=5 to 8 measurements per astronaut), 1.2% for fat-free mass (FFM) and 4.9% for fat mass (FM) (DXA n=3 measurements per astronaut; hydrometry n=1). Astronauts were considered in energy balance the year before flight.

The flight session started after at least three months onboard the ISS but not during the last month in space. The three to five-month window was selected to provide data for long-term spaceflight and to allow a full isotopic equilibration between the astronauts' body water and the ISS potable water system partly recycling wastes. On average the flight session was conducted after 108 days (SD 19) in space.

Sessions performed on the ground and inflight were strictly similar. During those sessions total energy expenditure (TEE), body composition, water turnover, resting metabolic rate (RMR), activity energy expenditure (AEE) and physical activity (PA) were measured.

Prior to the ground and flight sessions, dry runs of the experiments were conducted to train the astronauts on the difficulties and intricacies of the different steps of the protocol. Dry runs and ground experiments were performed at EAC. Inflight experiments were followed on real time from the ISS at the Toulouse Space Center (CADMOS, Toulouse, France) and Danish Aerospace Company (former DAMEC, Odense, Denmark). Ground and inflight experiments were realized under the supervision of ESA and CNES science officers in charge of the experiment and the investigators.

Total energy expenditure

Dose preparation

Clinical grade doubly labelled water (DLW) was purchased from Eurisotop (Saint Aubin, France). Four mother solutions of DLW were prepared. Two for the ground sessions and two for the inflight sessions. Mother solutions were prepared in 2011 and 2015. Mother solutions were filter-sterilized and stored at ambient temperature. Flight doses were shipped to ISS twice between 2011 and 2017. All flight doses were pre-filled in 60-mL luer-lock syringes (Plastipak BD®) on which a 0.22 µm sterilizing filter was mounted and sealed by airtight caps. Filled syringes were weighted to the nearest 10^{-3}g and numbered. They were further stored in individual plastic bags thermo-sealed to prevent isotopic exchanges. On the ground, syringes were weighted before and after ingestion to accurately determine the ingested amount. In flight, the amount of water ingested was taken as the amount filled and weighted in the syringe corrected for the loss of water in the filters (0.52 mL per filter (0.06), n=33 independent repeats).

On the ground, the astronauts ingested 3.0 g/kg total body water (TBW) of a pre-mixed dose of DLW providing 0.30 g/kg TBW from 10% enriched $H_2{}^{18}O$ and 0.15 g/kg TBW from 99% enriched ^2H_2O. These doses were calculated to provide about 30% more ^{18}O isotopes than classical studies to limit the influence of small changes in astronauts' isotopic backgrounds associated with any potential travels prior to the DLW session. The maximum enrichments above background at the 4hr post-dose were

1217.2 (SE 36.2) and 145.5‰ (8.0) for deuterium and 18-oxygen, respectively [‰ (delta per mil) = (R_{sample} / $R_{standard}$ – 1) * 1000 (with R being the ratio of heavy to light isotope)]. The final enrichments above background on day 10 were 523.8 (33.7) and 50.1‰ (3.7) for deuterium and 18-oxygen, respectively.

In flight, the same DLW dose was used for all astronauts to simplify the inflight handling of materials. This procedure was previously used and was shown to not affect accuracy of the DLW method (Blanc et al., 2002; Stein et al., 1999b; Trabulsi et al., 2003). The astronauts ingested 105.2 g of $H_2{}^{18}O$ from a mix of 10% and 97% enriched $H_2{}^{18}O$ and 16.7 g of 99% enriched ^2H_2O. The dose was calculated to provide 0.51g/kg TBW of $H_2{}^{18}O$ and 0.35 g/kg TBW of ^2H_2O for an 80kg astronaut. This dose was more than twice a typical dose on the ground to minimize the impact of changes in isotopic background onboard the ISS due to recycling. The maximum enrichments above background at the 4hr post-dose were 2077.5‰ (SE 96.9) and 221.0‰ (10.4) for deuterium and 18-oxygen, respectively. The final enrichments above background were 996.7‰ (56.6) and 87.5‰ (5.3) for deuterium and 18-oxygen, respectively. Therefore, none of the astronauts were underdosed in flight by the fixed dose procedure.

Sample procedure

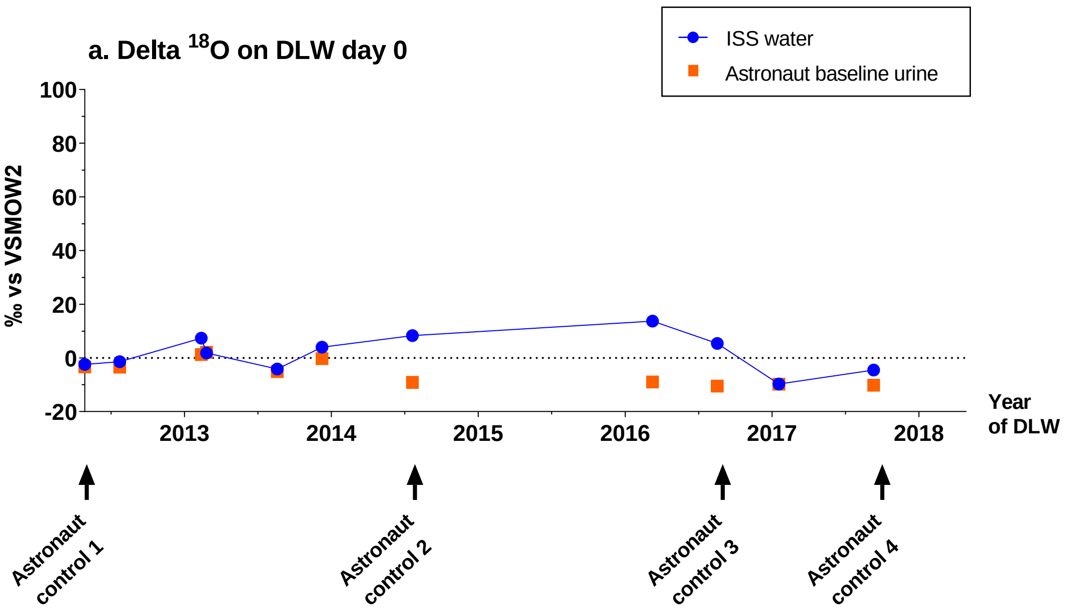
Before ingestion of the DLW dose, baseline urine samples were collected after an overnight fast. The mouth was rinsed with tap water after ingesting the dose and the bladder was emptied 1-hour post dose. Urine samples were then collected 4 and 5 hours post dose to assess the isotopic equilibration in body water. Any water drunk during the equilibration period was recorded and subtracted from TBW. For the next 10 days, the second morning voids were collected every other day in fasted state. The urines were immediately transferred to two 5mL plastic tubes with an O-ring seal (Corning®). Both tubes were further sealed in air-tight plastic bags and transferred into a 50mL Falcon tube (Falcon®) tightly sealed. Those procedures aimed to avoid contamination of the samples with the station vapor water. Urines were stored between 0.5 and 8°C on the ISS. The return of urine samples on Earth was realized at room temperature. They were immediately frozen upon landing and shipped to the CNRS IPHC isotope core facility for analysis.

Isotope recycling onboard the ISS

The water system of the ISS is different from the water system of the shuttles where water was produced by fuel cells. Fuel cells generated important fractionation in the isotopic composition of the potable water and the 2-week missions did not allow equilibration to the shuttle tap water enrichments. This is why the only two studies using DLW onboard the shuttles used DLW preloads and specific correction for background shift in tap water and recycling of isotopes (Lane et al., 1997b; Stein et al., 1999b). Onboard the ISS, the water is brought from the Earth and, in the US section, partly recycled from urines and wastewater. Recycled water is stored in tanks.

Due to the recycling, the ISS tap water background enrichment rises progressively over the time course of the study, i.e. between 2011 and 2017. This was checked by collecting a tap water sample at the beginning of each 11 inflight DLW session (**supplemental Figure 1**). Since the DLW sessions took place after at least 3 months in space, we checked isotopic equilibration between body water and the water station by following four control astronauts distributed throughout the study period (2011, 2014, 2016, 2017). Control astronauts were asked to follow the DLW protocol without being dosed. They drunk the same water source as the dosed astronauts. **Supplemental Figure** 1 shows compared enrichments of tap water and baseline urine of astronauts. Equilibration was good for 18-oxygen but derived with missions for deuterium.

To avoid recycling of isotopes during a DLW session, astronauts were asked to drink water from a full tank, i.e. not subjected to recycling. To check the stability of background enrichments during a DLW session, the control astronauts also provided urine samples at the same time points than the dosed subjects. These data showed that following this protocol enrichments of tap water and urines from control astronauts were stable during a DLW session (**supplemental Figure 2**). **Supplemental Figure 3** shows that deuterium tap water and body water still equilibrates during the DLW protocol. However, over the 10 days of the protocol the maximal change was 10‰, which was within the analytical range and compensated by the ingestion of a larger dose. Therefore, no correction for background shift was applied to the elimination rates as previously done during the two shuttle missions (Lane et al., 1997b; Stein et al., 1999b).



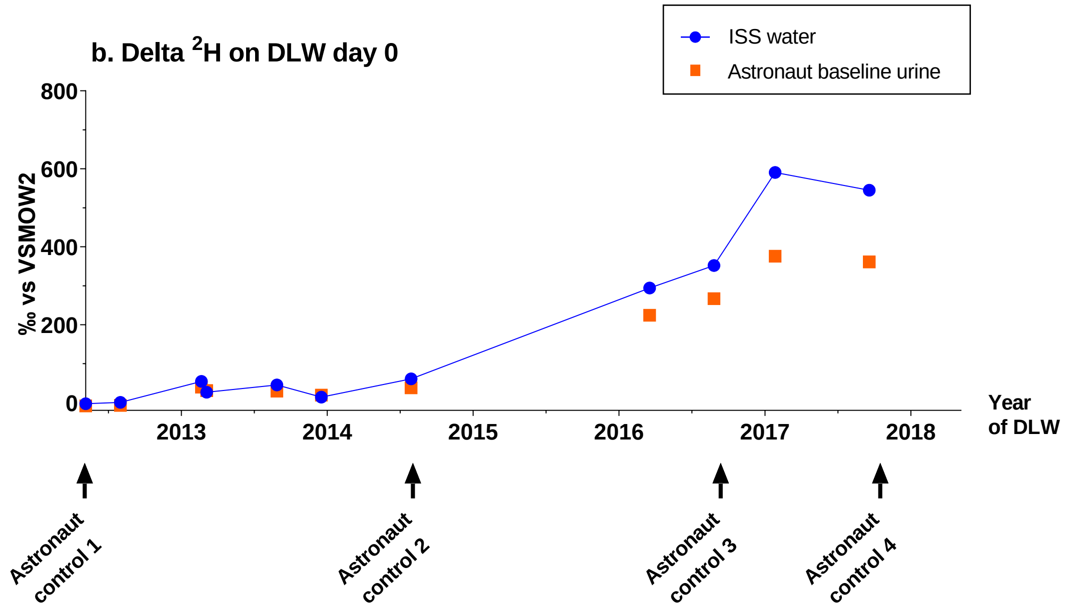


Figure 1: Verification of isotope (^{18}O and ^{2}H) stability for ISS water and control astronaut baseline urine against VSMOW2 IAEA standards at day 0 of the DLW period measurement.

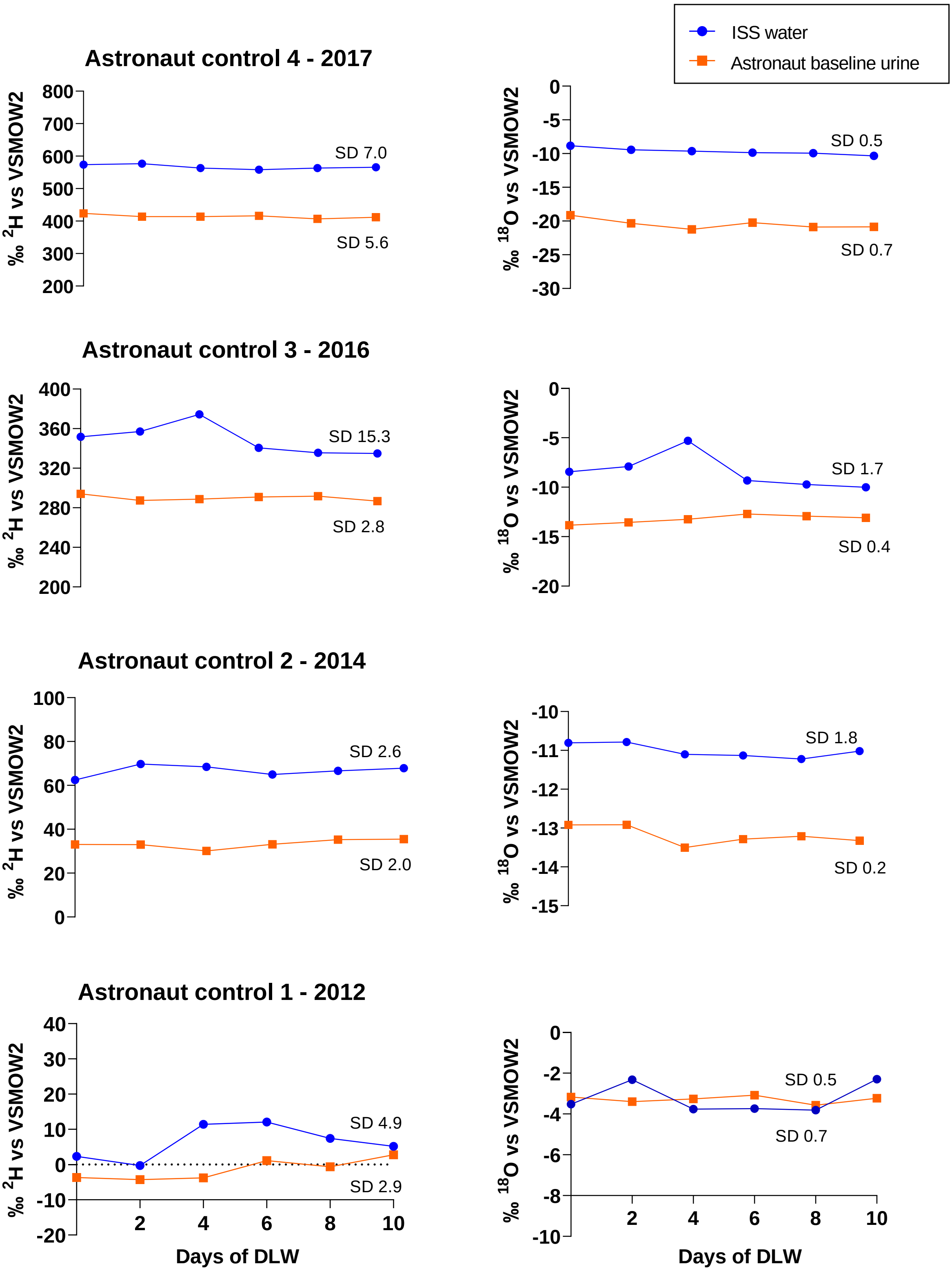


Figure 2: Verification of isotope (^{18}O and ^{2}H) stability for ISS water and control astronaut baseline urine against VSMOW2 IAEA standards during the DLW period measurement.

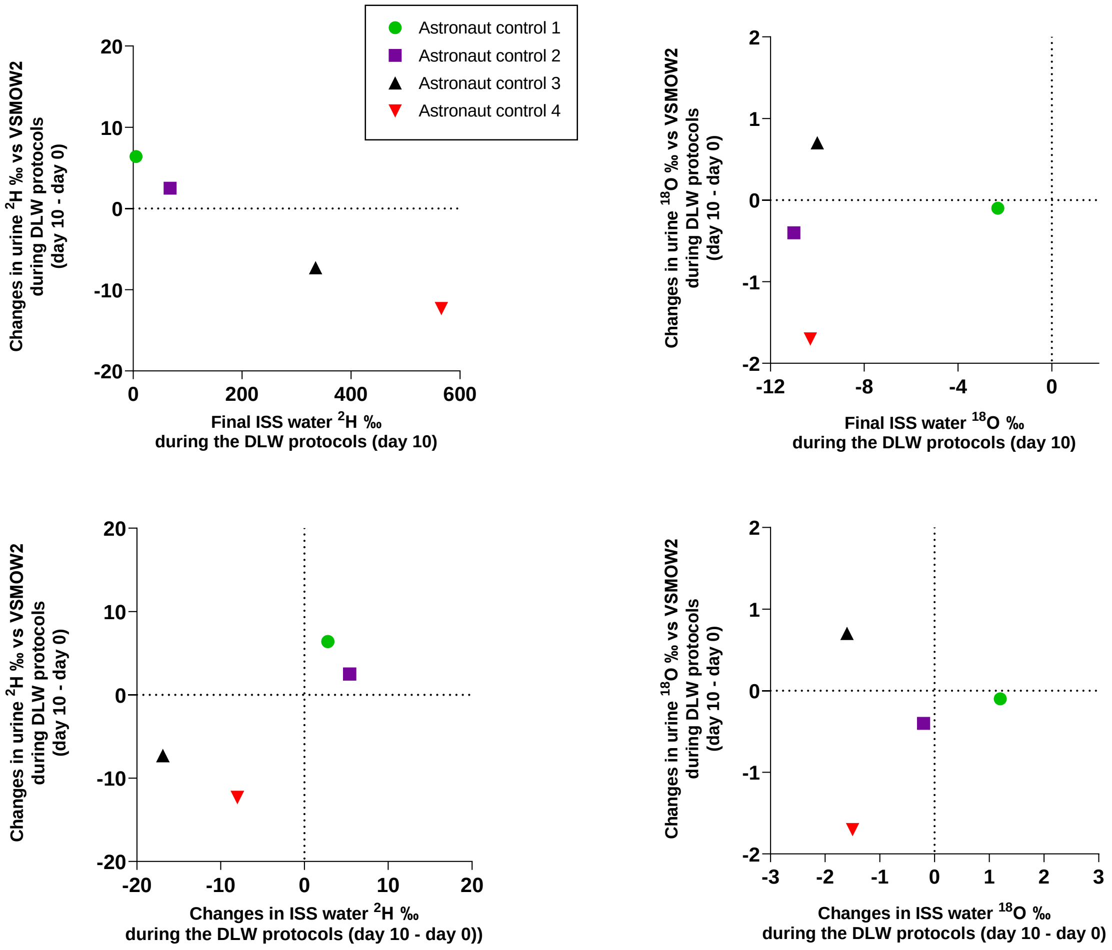


Figure 3: Stability of the ratio between ISS water isotopic level (upper row) and enrichment (lower row) at day 10 against changes in isotopic enrichment of control astronauts for ^{2}H and ^{18}O.

Sample analysis

Urines were cleaned with black carbon and filtered to extract water, as previously described (Chery et al., 2015). Extracted water was transferred to O-ring sealed vials and immediately analyzed by isotope ratio mass spectrometry. The determination of hydrogen and oxygen isotope ratios was performed using a high-temperature conversion elemental analyzer (TC/EA) interfaced with a Delta V Plus Isotope-Ratio Mass spectrometer and a Conflo III interface (THERMO, Bremen, Germany). The elemental analyzer was equipped with a bottom feed connector connected to a glassy carbon tube heated to 1400 °C under helium flux. The H_2 and CO generated by pyrolysis were separated with a GC column at 90 °C and measured during the same injection using magnetic jump mode to change masses. High purity hydrogen (N60) and carbon monoxide (N47) from Linde Gaz (France) were used as reference gases.

All samples from a single subject were analyzed in the same run. Due to the dose differences in isotope enrichments, inflight and ground sessions were not analyzed in the same run. Each sample was injected 10 times. First, five consecutive injections of the sample were injected at 2-min intervals without gas calibration to precondition the glassy carbon tube to the sample enrichment and limit memory effect from previous samples. Second five calibrated injections were performed. Results of the last four injections were average and reanalyzed when SD from quadruplets had SD>2‰ for ^{2}H and SD>0.2‰ for ^{18}O.

Four large batches of urine standards were prepared with enriched waters from Eurisotop (Saint Aubin, France) mixed with pooled human urine. The four enrichments span the body enrichments reached in our DLW studies. Urine standards were distillated and normalized against VSMOW2 and SLAP2 (IAEA, Vienna, Austria). Urine standards were treated as any biological samples to follow the same treatment principle and inserted at key enrichment transitions in the runs. Different standards were used to 1) correct memory effects, 2) have quality controls, and 3) normalize samples against the international scale (Chery et al., 2015).

Tap water samples were analyzed in separate runs in similar conditions except that they were not subject to black carbon filtration, and water standards were used instead of urine standards.

Astronauts were studied over 6 years between 2011 and 2017. Samples were analyzed immediately after each ground or inflight sessions. Analytical precision was assessed by repeating all isotopic analyses in 2018 using the remaining duplicate urine aliquots that were available for 10 out of the 11 astronauts. For TBW, the within-subject repeatability, calculated as the average percentage difference between the analyses performed immediately after landing and in 2018 was 0.3% (SD 0.1). The within-subject repeatability for TEE was 1.9% (0.7). The analytical precision taken as the geometric mean of the within-subject %CV was 0.7% for TBW and 4.0% for TEE. Results are within the limits of expectation predicted from the typical analytical variation in our laboratory, especially given the high enrichments reached during the flight sessions.

Calculations

TEE was calculated using the multi-point DLW approach. The dilution spaces for ^{2}H and ^{18}O were calculated from the baseline and equilibration samples according to Coward et al.(Coward et al., 1994). TBW was calculated from the average of the dilution spaces of deuterium and 18-oxygen after correction for isotope exchange by 1.041 and 1.007, respectively (Bhutani et al., 2015; Racette et al., 1994). ^{2}H and ^{18}O constant elimination rates were calculated by least-squares linear regression on the natural logarithm of isotope enrichments from all urine samples as a function of elapsed time from dose administration. CO_2 production was then calculated according to Schoeller et al.(Schoeller, 1988) modified by Racette et al.(Racette et al., 1994), and TEE was derived using Weir's equation (Weir, 1949) using a food quotient (FQ). On the ground, FQ was derived using the Black's formula using national nutritional surveys for each country of the 11 astronauts (Black et al., 1986). We used the average value of 0.872 to account for the fact that astronauts keep traveling in different countries for training and therefore have a 'mixed international diet'. Inflight FQ was calculated from the recipes of the recorded food ingested. Because those records were incomplete for several astronauts, the overall average for FQ, i.e. 0.869 was used for all astronauts.

Resting metabolic rate

On the DLW dosing day, RMR was measured in fasting state at rest for 45 min using the Pulmonary Function System (PFS, commissioned by ESA and manufactured by the Danish Aerospace Company (DAC, Odense, DK))(Moore et al., 2014). Participants were allowed to watch TV or listen to music, but not to sleep. The technology of the PFS was detailed by Moore et al.(Moore et al., 2014) which explains that the "PFS uses two types of technology for gas analysis. CO_2 is measured using a photoacoustic method of gas analysis and O_2 is measured using an Oxigraf model X2004 sensor (Oxigraf, Mountain View, CA). A custom designed two-way nonrebreathing valve was used to collect gases during inspiration, and the expired gases were sampled in a 15-L capacity anesthesia bag, which serves as a mixing reservoir. Ventilation was measured on the inspired side of the nonrebreathing valve using a custom-designed differential pressure flowmeter. The PFS gas analyzer module was calibrated before each RMR measurements using reference gases, and the flowmeter was calibrated with a 3-L volumetric syringe. Each PFS underwent stringent acceptance tests to validate instrument performance". Further informations regarding the technology used for metabolic gas analysis within the PFS are contained in a paper of Clemensen et al.(Clemensen et al., 1994). A proprietary software package (Agile Data Analyzer and Monitor (ADAM, DAC) was used to compute VO_2 and VCO_2 from the raw data. The first 10 min were excluded from all measurements. Stability of measurements were visually checked for each astronaut. RMR was calculated from the Weir's equation (Weir, 1949).

Body composition

Ground BM was measured on the day of DLW dosing using a scale while wearing undergarments. During the flight, the SLAMMD device (Space Linear Acceleration Mass Measurement Device) was used to assess BM within one day of the DLW dosing. In pre- and post-flight, FFM and FM were measured by DXA (Hologic, Marlborough, MA, USA; software versions 12.7.3.1 in 2011 to 15.5.3 in 2016). DXA measurements were realized as part of NASA Medical operations. FFM from DLW was calculated assuming a hydration coefficient of 73.2%. FM was calculated as the difference between BM and FFM. The agreement between the closest DXA and hydrometry data before flight, calculated as the average percent difference between the two methods was 1.2% (0.6) for BM, 0.1% (0.6) for FFM and 5.9% (2.1) for FM. Given that the DXA measurements were spread over the year before flight, there was a good agreement between the two methods.

Energy intake

Food intake was recorded by astronauts by scanning any food item ingested while on the ISS. Energy intake and macro-nutrient composition were afterwards calculated using recipes provided by space agencies. The data provided by NASA during this experiment were incomplete and did not allow to calculate with precision the energy intake (EI) during the DLW sessions. For example, some astronauts reported EI as low as 7MJ/d with meals and data missing. We therefore calculated EI from the changes in body composition and TEE between the two DLW sessions (Ravelli & Schoeller, 2021; Votruba et al., 2002). Calculated EI were compared with theoretical EI calculated with the modified formula

$EI = [662 - (9.53 \times age\ (y)) + PA \times [15.91 \times weight\ (kg) + 539.6 \times height\ (m)] \times$ 0.0042 (Institute of Medicine, 2005)

where PA is the physical activity coefficient of 1.45 for very active individuals and 0.0042 to convert kcal in MJ.

Physical activity and exercise

Physical training prescriptions

Historically the exercise countermeasure program has been centered on the prevention of microgravity-induced remodeling of physiological systems and health consequences. It has progressively evolved to help astronauts reaching the fitness level necessary for the performance of routine and unexpected mission tasks (Hackney et al., 2015). During these spaceflights, six days a week, 2.5 h/day were allotted in crew schedules for inflight exercise, including equipment set-up, data transfer and clean-up (Hackney et al., 2015; Loehr et al., 2015) Aerobic exercise, prescribed as 30-45 min / sessions, was performed using self-selected exercise protocols based upon the preflight astronaut's cardiovascular fitness and adapted to flight phase, either on the cycle ergometer (CEVIS) or on a treadmill (T2) with vibration isolation system (**Supplemental Fig 4**). The CEVIS operates from 0 to 350 W. The T2 has a maximum speed capability of 20.4km/h (Scott et al., 2019). During treadmill exercise, an external vertical load (60-100% of body weight) was applied to the astronaut through a harness to partially compensate for the absence of body weight in microgravity environment. The resistive exercise sessions were realized on the advanced resistive exercise device (ARED) (Supplemental Fig 4) that has a load capability of 272 kg (Scott et al., 2019). The prescription, which slightly varied according to agencies (Loehr et al., 2015), consisted of 3 to 4 workouts composed of 5 to 7 exercises, primarily focused on the lower body, with 3 variations for intensity levels (light, medium, high) using 8 to 15 repetitions for 3 to 4 sets. Loads were individually adapted throughout the flight with an on-earth conditioning, and rehabilitation specialist paired to each astronaut. Because BM does not contribute in resistance in microgravity environment, this was added to the external load target.

Physical training logs

Parameters of inflight exercise training, actually performed during spaceflight, were obtained from prospective self-reported exercise logs provided by NASA. These logs included date, duration, average speed and external load of treadmill sessions; date, duration, average power and revolution per min (rpm) of CEVIS sessions; date and detailed exercise series workouts, including for each of them the number of sets and repetitions and absolute loads of ARED sessions. Mean daily and weekly exercise parameters over a time period, beginning 2 months before the experimental flight session and including this latter, were calculated and are presented descriptively. An estimation of treadmill exercise power (in Watts) was calculated using the American College of Sports Medicine (ACSM) formulas (American College of Sports Medicine, 2000) from speed and external load (instead of body mass). For both T2 and CEVIS weekly exercise workloads (W.h) were calculated as power*weekly duration. For resistance exercise, total weekly repetitions (sets*repetitions), average load per repetition (kg) and weekly volume loads (sets*repetitions* loads) were calculated (English et al., 2020). As the duration of workloads were not provided in the logs, for comparison with the activity device-derived data, muscular time under tension during resistance exercise was calculated based on the number of repetitions, assuming a 2-to-5 s count for each repetition (i.e. including both concentric and eccentric phases), according to movement complexity from online video featuring this kind of exercise (Trappe et al., 2009). An additional 1-min resting time by set was added to obtain an approximation of weekly time involved with resistance exercise on ARED (**Supplemental Figure 4** and **Supplemental Table**).

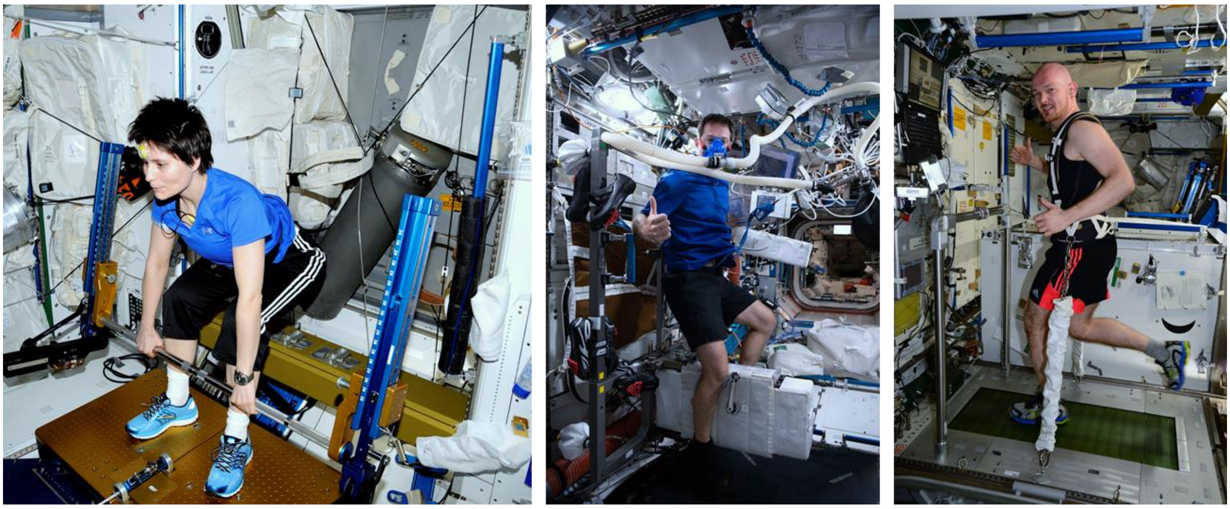


Figure 4: Hardware used for exercise countermeasures. From left to right: ESA astronaut using the Advanced Resistive Exercise Device (ARED) on the International Space Station (copyright: ESA/NASA); ESA astronaut using the Cycle Ergometer with Vibration Isolation and Stabilization System (CEVIS) on the International Space Station (copyright: ESA/NASA); ESA astronaut using the T2 treadmill on the International Space Station (copyright: ESA/NASA).

Sensewear Pro (SWP) and accelerometry

PA was further estimated using the Sensewear Pro (SWP), an activity multi-sensor armband including a bi-axial accelerometer (Body media Inc®, Pittsburgh, PA USA), worn on the non-dominant arm throughout the two DLW sessions. Its companion software (professional version 8.0), which incorporates a proprietary machine-learning activity classification algorithm based on heat flux, galvanic skin response, skin and near-body ambient temperature and accelerometry measures patterns (Andre et al., 2006), was used to identify non-wear periods and, after exclusion of non-valid days, obtain steps and categorize each minute in activity classes. As the detailed activity-classification algorithm has not been validated in microgravity environment, only 4 classes were retained for this study: inactivity, walking, running and all other detected physical activities as “non-ambulatory physical activities”. We validated the running class during the experimental inflight period by comparing SWP-derived running and self-reported T2. A moderate agreement (Concordance correlation coefficient (CCC)=0.64) was found between the two measures of running time with a high correlation (R^2=0.89) between reported T2-workload and running-MAD.

The norm of the one-min acceleration signal mean amplitude deviation (MAD) (Vähä-Ypyä et al., 2015a), that removes the static component due to gravity from the raw signal in order to only keep the dynamic component due to body movements and changes in velocity, was used as an additional indicator of PA workload and intensity. MAD is a validated method to estimate the intensity of PA that has been related to heart rate or VO_2 during exercise (Vähä-Ypyä et al., 2015a; Vähä-Ypyä et al., 2015b). Aggregation of one-min MAD that corresponds to the product of duration by one-min intensity is considered as a composite proxy of workload of a given effort/exercise bout or of overall daily PA (Vähä-Ypyä et al., 2015a). It was expressed in milli-g (i.e. 0.001 g) for a given period. Sensewear-derived vigorous PA was estimated using a MAD-cutpoint of 16 milli-g/min.

Supplemental Table

Table: Self-reported characteristics of inflight physical training over a 2-month period by inflight-TEE-evolution groups.

	All astronauts (n=11)	**Astronauts with stable TEE (n=6)**	**Astronauts with decreased TEE (n=5)**	**P Value**
Aerobic Training				
Aerobic exercise (Treadmill & CEVIS)				
Session number per week	6.2 (1.4) [3.5-8.6]	6.5 (1.5) [4.8-8.6]	5.8 (1.4) [3.5-7.1]	0.43
Session duration (min)	27.04 (3.88) [22.95-35.89]	27.89 (4.93) [23.14-35.89]	26.03 (2.21) [22.95-27.94]	0.46
Weekly duration (min)	167.77 (43.90) [86.85-257.81]	180.28 (43.97) [125.46-257.81]	152.76 (43.42) [86.85-192.87]	0.33
Average power (W)	144.77 (43.46) [81.55-221.18]	168.16 (42.99) [121.15-221.18]	116.69 (24.62) [81.55-137.22]	0.04
Weekly workload (W.h)	427.10 (231.25) [217.47-967.48]	531.69 (262.48) [252.32-967.48]	301.59 (107.13) [217.47-426.30]	0.10
Treadmill (T2)				
Session number per week	3.6 (1.1) [1.3-5.5]	4.1 (0.9) [3.2-5.5]	2.9 (1.0) [1.3-3.7]	0.07
Session duration (min)	25.57 (6.61) [13.00-40.51]	27.38 (7.07) [21.86-40.51]	23.40 (5.99) [13.00-27.30]	0.35
Weekly duration (min)	93.20 (31.87) [16.66-135.79]	110.13 (20.78) [83.42-135.79]	72.88 (32.46) [16.66-99.59]	0.05
Average speed (km/h)	9.96 (2.02) [4.83-12.36]	11.17 (0.85) [10.07-12.36]	8.50 (2.09) [4.83-9.82]	0.02

Average load (kg)	53.73 (14.45) [34.29-77.00]	60.45 (14.39) [42.74-77.00]	45.66 (10.68) [34.29-59.00]	0.09
Average percentage load (body mass percentage)	68.25 (13.66) [52.50-95.42]	73.43 (16.13) [57.20-95.42]	62.03 (7.25) [52.50-69.69]	0.18
Average power (W)	140.92 (57.51) [73.91-250.64]	177.27 (52.21) [128.82-250.64]	97.30 (22.38) [73.91-121.69]	0.01
Weekly workload (W.h)	235.98 (149.46) [20.52-520.34]	331.10 (134.41) [179.09-520.34]	121.84 (58.41) [20.52-162.99]	0.01
CEVIS				
Session number per week	2.6 (0.9) [1.5-4.1]	2.4 (0.9) [1.5-4.0]	2.9 (0.9) [2.1-4.1]	0.41
Session duration (min)	27.99 (3.36) [21.73-33.23]	28.34 (3.53) [23.69-33.23]	27.57 (3.50) [21.73-30.95]	0.73
Weekly duration (min)	74.57 (30.83) [37.58-134.31]	70.15 (34.56) [37.58-134.31]	79.88 (28.63) [44.99-113.57]	0.63
Average power (W)	145.99 (38.90) [84.22-221.24]	157.84 (41.51) [104.48-221.24]	131.77 (34.15) [84.22-174.47]	0.29
Weekly workload (W.h)	191.11 (121.55) [73.22-495.23]	200.59 (153.38) [73.22-495.23]	179.75 (85.03) [87.50-263.32]	0.79
Resistance Training				
Total resistance exercise (ARED)				
Session number per week	4.5 (1.8) [1.8-6.6]	4.3 (2.0) [1.8-6.6]	4.7 (1.8) [2.8-6.5]	0.75
Exercise number per session	9.33 (1.23) [5.89-10.20]	9.91 (0.18) [9.70-10.19]	8.64 (1.62) [5.89-9.92]	0.09
Set number per exercise	2.86 (0.26) [2.20-3.20]	2.95 (0.15) [2.80-3.20]	2.75 (0.33) [2.20-3.05]	0.22

Repetitions per set	12.30 (1.98) [8.79-15.11]	12.33 (1.61) [10.66-15.11]	12.27 (2.56) [8.79-14.58]	0.97
Weekly total repetitions	1481 (834) [468-3044]	1592 (941) [594-3044]	1347 (770) [468-2407]	0.65
Muscle under tension time per week (min)	81.82 (43.50) [28.78-161.23]	88.37 (48.63) [33.99-161.23]	73.97 (40.39) [28.78-132.98]	0.61
Weekly duration per week including recuperation time (min)	203.12 (100.20) [75.81-365.02]	216.13 (112.48) [83.88-365.02]	187.50 (93.40) [75.81-322.37]	0.66
Average load per repetition (kg)	63.49 (15.13) [40.13-86.83]	63.70 (16.02) [40.13-85.88]	63.23 (15.86) [44.82-86.83]	0.96
Weekly load (kg)	95581 (64510) [24822-224754]	110855 (81613) [24822-224754]	77253 (36168) [39608-135454]	0.42

Data are means (SD) [minimum-maximum].
Weekly aerobic exercise workload (W.h) was calculated as power * weekly duration; weekly resistance exercise load (kg) was calculated as average load per repetition * repetitions/week.
squat = back squat, single leg squat, and sumo squat; heel raise =heel raise and single leg heel rise; deadlift=deadlift, Romanian deadlift and sumo deadlift

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Chapitre 6. Physiological adaptations in women during a North Pole expedition: the POWER study

1. Résumé

Bien que la majorité des études sur la régulation de la balance énergétique en milieu extrême concernent les hommes, très peu de données ont été collectées chez les femmes. L'étude POWER, incluant onze femmes non-athlètes participant à l'expédition Women Euro-Arabian North Pole Expedition 2018 avait pour but de mesurer pour la première fois les besoins énergétiques des femmes et comprendre les adaptations des différentes composantes de la balance énergétique au cours d'une expédition polaire visant à rejoindre le Pôle Nord en ski en autonomie totale. L'hypothèse était que l'activité physique élevée en condition extrême induirait une dépense supérieure aux apports énergétique et donc une balance énergétique négative, se traduisant par une perte de masse corporelle majoritairement due à une perte de masse grasse.

La dépense énergétique totale a été mesurée par eau doublement marquée sur la totalité de l'expédition, et le MR a été mesuré avant et après l'expédition. La composition corporelle a également été mesurée avant et après l'expédition par dilution isotopique. L'accélérométrie 3D a permis de mesurer et identifier les patterns d'activité physique, et le couplage à la fréquence cardiaque d'estimer l'intensité des activités.

Les contraintes logistiques et environnementales ont induit une dépense énergétique très élevée chez les femmes ayant rejoint le Pôle Nord en ski comparativement à celle observée dans une population similaire en condition de vie libre, avec un niveau d'activité physique deux fois plus élevé. Le haut niveau d'activité physique requis lors de l'expédition a induit une augmentation de la masse maigre au dépend d'une perte de masse grasse en une semaine seulement ; la masse grasse permettant de fournir l'énergie nécessaire aux besoins de l'expédition dans une situation de balance énergétique négative. Bien que l'activité physique mesurée par n'ait mesuré que des activités d'intensité légères en raison des faibles accélérations corporelles, la fréquence cardiaque et la mesure de la DETJ élevées suggèrent un coût plus important de l'activité physique en milieu polaire, dû aux nombreuses contraintes exercées par cet environnement extrême (e.g. lutte contre le froid et les vents extrêmes, combinaisons encombrantes, tractage du traineau, etc.).

2. Manuscrit

Physiological adaptations in women during a North Pole expedition – the POWER study

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Abstract

Background: Polar expedition represents a major challenge at the origin of moderate to severe energy deficit. While most of the studies investigated energy requirements of athletes or military personals, few data exist on non-professional individuals. More specifically, none of them investigated the regulation of energy balance in female participants during an Artic expedition.

Methods: We studied twelve non-athlete female adults who participated in the Women's Euro-Arabian North Pole Expedition 2018 that aimed to reach the North Pole by ski in full autonomy. Before and the day after the expedition resting metabolic rate (RMR) was measured by indirect calorimetry, and fat mass (FM) and fat-free mass (FFM) by bioelectric impedance. Total energy expenditure (TEE) and activity-related energy expenditure (AEE) were assessed with the doubly labelled water (DLW) during the expedition. Before and throughout the expedition, daily physical activity was evaluated by actigraphy, surface skin temperature by i-Button placed on the chest, and fasting salivary cortisol concentration was measured throughout the expedition as a stress marker.

Results: The participants covered about 100 km on ice and reached the North Pole in 7 days. This was associated with a DLW-derived TEE of 18.67 [SD 1.72] MJ/d, which was 107% higher than their estimated TEE from resting metabolic rate. Body mass decreased by 1.67 (SE 0.42) kg mostly due to fat mass loss (-1.26 [0.39] kg), indicating a negative energy balance

Conclusion: Non-athlete females are able to greatly increase their AEE and hence TEE over short time-period. However, their food consumption was not sufficient to cover their needs thus leading to energy deficit and body mass loss. Future studies will need to determine whether this insufficient energy intake was due to insufficient available food or incapacities to eat more.

Introduction

Polar areas are extreme environments because of their topology and severe climate (Cotter & Tipton, 2014). While several teams attempted to conquer the Poles and break records during the “heroic age” of polar exploration (1895-1922) (Leon et al., 2011), emaciation was commonly observed with various effects ranging from ill health to death (Halsey et al., 2015). Body mass loss can only result from insufficient energy intakes (EI) to cover energy requirements. This imbalance can be due to total daily energy expenditures (TEE) too high to be covered by food intake, and/or insufficient available food.

Arctic regions offer a unique set of challenges and hazards including extreme temperatures, blizzards and difficult terrain due to the ice always on the move (crevasses and frozen lakes, channels of open water). Individuals who are non-native from cold weather regions are particularly vulnerable to heat loss, which can have major deleterious consequences on metabolic, cardiovascular, respiratory or immune functions (Færevik et al., 2013; Frank, 2001; Leon et al., 2011). Thus, organisms need to acclimatize to ensure performance, health, and survival (Halsey & Stroud, 2012). Physiological compensatory mechanisms are triggered to maintain core temperature at thermoneutrality including vasoconstriction, shivering or brown-adipose tissue mobilization (Leppäluoto & Hassi, 1991; Yurkevicius et al., 2022). However, these physiological compensatory mechanisms are at the origin of a cold-induced thermogenesis, partly observed through an increase in resting metabolic rate (RMR) (Haman & Blondin, 2017; Kulterer et al., 2020b; Ouellet et al., 2012). In parallel, the use of high-performance polar suits alter locomotor efficiency, thus increases workload, and to extent activity-related energy expenditure (AEE) of up to 16% (Holmer, 2009; Teitlebaum & Goldman, 1972). Stress associated with polar environmental-related dangers and sleep alterations (polar bear watches to prevent attacks, long day light) should also be taken into account in energy requirements since they are known to increase energy expenditure (Chaput et al., 2023; Rabasa & Dickson, 2016).

In addition to these environmentally challenging constraints, Arctic deep access is restricted to walking or cross-country skiing with self-carrying sledges containing food, clothes and tents due to the geography and remoteness of the area. This leads individuals to optimize their sledge and the choice of food rations by finding the best compromise between the mass of the rations, and their energy density (Ahmed et al., 2020; Charlot, 2021). However, an inadequate nutrition during arctic expeditions often undermined the integrity of the crew, that can jeopardize the expedition and even dramatically provoke death (Halsey & Stroud, 2012). To optimize nutrition during such expeditions, it is vital to accurately measure the energy needs. To date, only few studies have been conducted in Polar regions, on relatively small samples and essentially in Antarctica (Hattersley et al., 2019b; Iuliano & Ayton, 2015; Stroud, 1998). In addition, there are only very rare studies in women thus limiting the generalization of data (Hattersley et al., 2020; Hattersley et al., 2019a; Paulin et al., 2015), and none in women during Arctic expedition.

This gap in knowledge needs to be filled to better understand energy balance regulation during polar expeditions and allow women crew to safely and successfully reach new horizons. In April 2018, an all-female team of 12 European and Middle Eastern explorers skied the last degree to the North Pole. The initial goal of this expedition was to foster greater dialogue and bridge the gap between East and West. From a scientific point of view, the expedition was an exceptional opportunity to better understand the physiological adaptations of females to polar regions. The POWER study aimed to determine TEE and its components (i.e. AEE and resting metabolic rate – RMR), and body composition changes during the expedition to assess energy balance status. Other behavioral and biological factors known to influence TEE were directly or indirectly assessed as daily physical activity, stress and thermoregulation.

Materials & Methods

Participants

Twelve non-athlete women who took part to the Women's Euro-Arabian North Pole Expedition 2018 voluntary took part in the present study. Because the POWER study was an addition to the already planned expedition, no inclusion or exclusion criteria were formulated. Participants were free to accept or decline the participation in the POWER study, and withdraw from it at any time without any impact on their participation in the expedition. Baseline analyses were collected on 11 participants. One had to be evacuated by helicopter after 2 days of expedition because of frostbites.

The study was approved by the Colorado Multiple Institutional Review Board under the number COMIRB 17-2144. A written informed consent was obtained from all participants.

Protocol

Between 14 and five days prior to the start of the expedition, participants met in Longyearbyen, Svalbard, Norway with the scientific team to get a briefing about the study and the expedition, and perform baseline data measurements. Then participants flew in a cargo airplane on April 14th, 2018 to

Camp Barneo, a private temporary tourist resort located on Arctic Ocean ice near the North Pole. The expedition aimed to reach the geographic North Pole in full autonomy skiing, pulling their sledges containing their own food, clothes and ice tents for the entire trip. Participants covered a distance of 60 nautical miles (approximately 100km) in 7 days and reached the North Pole on April 22nd, 2018.

Data collection was performed at the Longyearbyen Hospital before and the day after their return to Longyearbyen, i.e. one day after they reached the North Pole. Body mass and composition and RMR were measured before and after the expedition. Free-living TEE was measured with the doubly labelled water (DLW) method during the expedition. As soon as they arrived in Longyearbyen, they were equipped with loggers to measure continuously their daily physical activity and skin surface temperature. They were given new monitors the day prior their departure to Camp Barneo, and were asked to wear them during the whole expedition.

Body mass and composition

Participants were weighted before and after the expedition in undergarments after an overnight fast using a standard scale. Fat-free mass (FFM) and fat mass (FM) were measured with bioelectric impedance (BC-601 Body Composition Monitor, Tanita, Tokyo, Japan).

Total energy expenditure

Baseline habitual free-living TEE was estimated as an average of the measured resting metabolic rate (RMR) before the expedition multiplied by an activity factor of 1.5 (Westerterp et al., 2021). TEE during the expedition was determined with the doubly labelled water (DLW) method over an 8-day period corresponding to the day prior to the expedition and the 7 days of expedition. On the morning the day prior to the start of the expedition, participants ingested a premixed 2.68 g/kg estimated total body water (TBW) composed of 0.33 g/kg TBW $H_2{}^{18}O$ enriched at 13.4% and 0.22 g/kg TBW of ${}^2H_2O$ enriched at 99.9% (Eurisotop, Saint-Aubin, France) to provide a sufficient enrichment during high water turnover rates. Urines were collected 4 and 5 hours after dose ingestion to calculate equilibration (Blanc et al., 2002), and then after the expedition at day 9 and day 9+1h.

Urines were cleaned with black carbon and filtered to extract water, as previously described (Chery et al., 2015). The determination of hydrogen and oxygen isotope ratios was performed using a high-temperature conversion elemental analyzer (TC/EA) interfaced with a Delta V Plus Isotope-Ratio Mass spectrometer and a Conflo III interface (THERMO, Bremen, Germany). Results were scaled using two internal laboratory standards normalized against international standards versus the VSMOW2/SLAP2 scale (International Atomic Energy Agency, Vienna, Austria). Analyses were performed in quadruplicate and repeated if the SD exceeded 2% for deuterium and 0.2% for 18-oxygen.

TEE was calculated using the multi-point DLW approach. The dilution spaces for ^{2}H and ^{18}O were calculated from the baseline and equilibration samples according to Coward et al. (Coward et al., 1994). Total body water (TBW) was calculated from the average of the dilution spaces of deuterium and 18-oxygen after correction for isotope exchange by 1.041 and 1.007, respectively (Bhutani et al., 2015; Racette et al., 1994). ^{2}H and ^{18}O constant elimination rates were calculated by least-squares linear regression on the natural logarithm of isotope enrichments from all urine samples as a function of elapsed time from dose administration. CO_2 production was then calculated according to Schoeller et al. (Schoeller, 1988) modified by Racette et al. (Racette et al., 1994), and TEE was derived from the Weir's equation (Weir, 1949) using a food quotient (FQ). Macronutrient composition was extracted from each prepacked meal to calculate the FQ of each meal using Black's formula (Black et al., 1986), and the average FQ was used for TEE calculation.

Because of the change in isotopic enrichment of water during the expedition, ice was collected each day to correct for background isotopic enrichment. In addition, a control participant was asked to follow the DLW protocol without being dosed, meaning she provided urine samples at the same time points than the dosed subjects to correct for changes in background isotopic enrichment leading to a sample of 10 dosed participants.

Resting metabolic rate and activity-related energy expenditure

RMR was measured with indirect calorimetry (Fitmate, COSMED, Rome, Italy) during a 25-minute period, the 5 first minutes being excluded from the analyses to keep a stable state. Subjects were lying down, awake, at thermoneutrality and were asked to not talk. Physical activity level (PAL) was calculated as the ratio of TEE by RMR. AEE was calculated as 0.9*TEE-RMR, 10% of TEE being estimated to be the diet-induced thermogenesis, i.e. the energy cost of food processing (digestion, assimilation, use, storage).

Energy intake and energy balance

Energy intake (EI) was estimated from the changes in body composition and TEE between baseline and post-expedition measurements sessions (Ravelli & Schoeller, 2021). Energy balance (EB) was calculated from the difference between EI and TEE.

Skin temperature

Skin temperature was continuously recorded before and during the expedition with loggers (iButton Temperature, DS1922L, Sunnyvale, CA, USA) strapped on the chest. Two i-buttons were also strapped on two different sledges to measure ambient temperatures.

Physical activity

Daily physical activity was evaluated using tri-accelerometers ActiGraph GT3x+ worn on the waist (ActiGraph®, Pensacola, FL, USA) during the baseline period (4-7 days) and during the expedition (5-10 days). The companion ActiLife software V.6.4.3 was used to obtain daily vector magnitude in counts per minutes (VM, cpm) as a proxy of overall physical activity, light-, moderate-, and vigorous-accelerations-related physical activities using cut-off as previously described (De Jong et al., 2018). Because participants had to carry very heavy load on a difficult terrain, their walking pace was relatively slow thus translating into light/low acceleration. However, these light accelerations cannot be associated with light-intensity physical activities. This is why we categorized the physical activities being related to light, moderate and vigorous accelerations instead of using the term “intensity” that refers to an estimated volume of oxygen consumption as traditionally done in studies with accelerometers.

Salivary cortisol

From the day before the expedition, every morning during the expedition and the day after the expedition, participants were asked to collect in duplicate saliva samples using two salivettes tubes immediately upon waking up and 30 min after for cortisol measurement. This was done in the morning before standing up while still in bed or in a sleeping bag. Saliva cortisol was measured with an ELISA kit

(Salimetrics, CA, USA). Intra- and inter-assay precision were 3-7% and 3-11%, respectively, and analytical and functional sensitivity were 0.007 µg/dL and 0.028 µg/dL, respectively. Mean value of both concentrations was used in the analyses.

Statistical analyses

Visual inspection of the histogram of residuals and analysis of Kurtosis and Skewness indexes, as Shapiro-Wilk tests were used to determine if data were normally distributed. Linear mixed-model accounting for repeated measurements (i.e. pre- vs post-expedition) with indicator for the time as fixed effect were used to test the specific effect of the polar expedition on the variables, and a compound-symmetric covariance structure was used to account for the dependencies among measurements. Our statistical inference was the effect of time. General linear models were used to examine the associations between baseline anthropometric outcomes (BM, FFM and FM) and their changes induced by the expedition.

Baseline values are presented as means (standard deviation, SD). Otherwise indicated, other data are presented as least squared means (standard error) (LSmeans [SE]) or with their 95% Confidence Interval (CI). Statistical inferences were on changes induced by the expedition (i.e.¸delta between baseline and post-expedition). Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) with a significance level at 5%. Figures were realized with Prism 9.3 (GraphPad, San Diego, California).

Results

Baseline characteristics of participants

Eleven women aged 36.9 (SD 6.7; range: 28 – 49 years old) completed the study. Women were normal-weighted with a mean body mass index of 24.2kg/m² (3.4) (range: 21.6 to 30.7 kg/m²). They had a fat-free mass index of 15.8 kg/m² (1.0) (range: 14.5 to 17.5 kg/m²) and a fat mass index of 7.5 kg/m² (2.7) (range: 5.2 to 13.2 kg/m²). Mean adiposity was 30.4 % (6.1) ranging from 23.8 to 43.5% (**Table 1**). Before the expedition while in Svalbard, participants spent 14. 57 h/day (3.37) in sedentary activities. Time spent in light-, moderate- and vigorous-acceleration derived physical activities was 1.30 h/day (0.23), 1.42 h/day (0.16) and 0.11 h/day (0.08), respectively. Measured RMR was 6.10 MJ/d (1.00), and we estimated an averaged baseline TEE of 9.14 MJ/d (1.51), and AEE of 2.13 MJ/d (0.35).

Table 1: Baseline characteristics of the participants.

	n	Mean (standard deviation)	Minimum – Maximum
Demographic outcomes			
Age (year)	11	36.9 (6.7)	28.0 – 49.0
Height (m)	11	1.66 (0.07)	1.57 – 1.77
Anthropometric outcomes			
Body mass (kg)	11	66.63 (12.33)	55.00 – 94.80
Fat-free mass (kg)	11	43.45 (4.38)	35.70 – 50-80
Fat mass (kg)	11	20.85 (8.56)	13.30 – 41.24
Fat mass (%)	11	30.41 (6.14)	23.80 – 43.50
Body mass index (kg/m²)	11	24.21 (3.40)	21.59 – 30.71
Fat-free mass index (kg/m²)	11	15.84 (1.04)	14.83 – 17.48
Fat mass index (kg/m²)	11	7.53 (2.69)	5.18 – 13.16
Energetic outcomes			
Estimated total energy expenditure (MJ/d) [a]	10	9.15 (1.51)	6.59 -12.01
Estimated activity-related energy expenditure (MJ/d) [a]	10	2.13 (0.35)	1.54 – 2.80
Resting metabolic rate (MJ/d)	10	6.10 (1.00)	4.40 – 8.01
Accelerometer-related physical activities			
Light accelerations-related activities (h/day)	9	1.29 (0.23)	0.91 – 1.58
Moderate accelerations-related activities (h/day)	9	1.42 (0.16)	1.14 – 1.67
Vigorous accelerations-related activities (min/day)	9	6.42 (4.99)	2.17 – 17.08
Sedentary behavior (% of daily activities)	9	82.72 (4.35)	74.20 – 88.51

Values are mean (SD).

Expedition-induced changes in body mass and composition

During the expedition, body mass decreased by 1.67 kg (SE 0.42) (95% CI -2.63 to -0.71), mostly due to loss of FM (-1.26 kg [0.38]; 95% CI -2.13 to -0.39). No significant change was observed in FFM (-0.43 kg [0.53]; 95% CI -1.64 to 0.77) (**Figure 1**, **Table 2**). These changes represented a relative body mass loss of 2.42% (SD 1.74), and FM loss of 6.45 % (7.21) compared to pre-expedition values. Regressions showed that body mass loss was negatively associated with baseline body mass ($R^2=0.53$; $P=0.02$). However, baseline fat mass did not explain FM loss ($R^2=0.01$; $P=0.78$) (**Figure 2**).

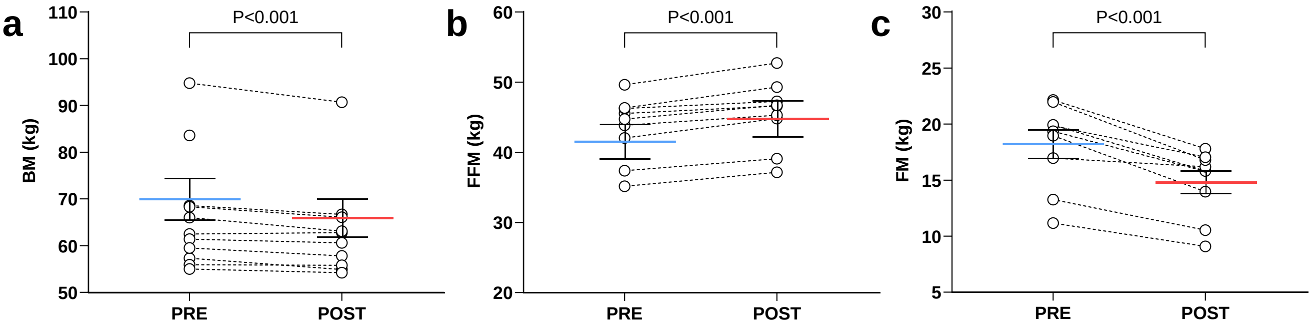

Figure 1: Evolution of body mass (BM), fat-free mass (FFM) and fat mass (FM) during the 9-day expedition. Individual data are presented with their least square means (standard error) from mixed-effects model for repeated measurements.
*** P<0.001

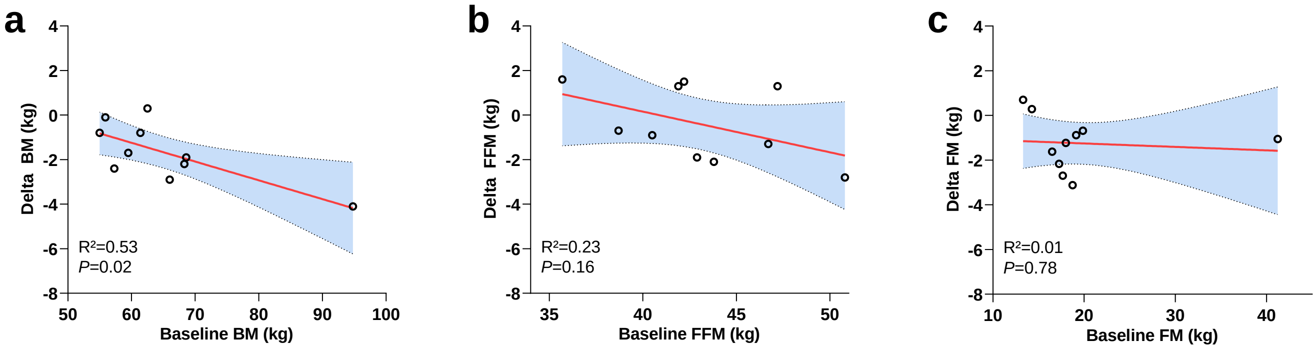

Figure 2: Associations between changes in anthropometric outcomes and baseline anthropometric outcomes. Least square regression line is plotted with the 95% confidence interval in shaded area.
BM= body mass, FFM= fat-free mass, FM= fat mass.

Daily physical activity, energy expenditures and energy intakes during the expedition

Compared to the pre-expedition period, light (+4.82 h/day [SE 0.30], 95% CI 4.15 to 5.49) and moderate (+0.73 h/day [0.32], 95% CI 0.01 to 1.45) accelerations-related activities increased, while time spent in vigorous accelerations-related activities (-0.08 h/day [0.02], 95% CI (-0.14 to -0.03) was unchanged. Time spent in sedentary behaviors decreased by 23.2 % (2.0) (95% CI -27.7 to 18.8).

During the expedition, the team had very high levels of energy expenditure with an average daily DLW-derived TEE of 18.66 MJ/d (SD 1.72), that was mostly explained by a high AEE (10.76 MJ/d [1.34]). PAL during the expedition was 3.1 (0.2). RMR after the expedition was 6.25 MJ/d (SE 0.29), and not different from baseline value (estimated change: +0.15 MJ/d [SE 0.19]; 95% CI -0.27 to 0.58) (**Table 2**).

Based on body composition changes, daily energy intake was estimated to be 13.00 MJ/d (SD 5.59) on average during the expedition. This was insufficient to cover the very high energy needs. Participants were in negative energy balance of -5.66 MJ/d (5.09) (EB vs 0, *P*=0.004).

Table 2: Changes induced by the expedition.

	n	LS means during the expedition (standard error)	Estimated change from baseline (standard error)	95% Confidence interval	P-value
Anthropometric outcomes					
Body mass (kg)	11	64.96 (3.60)	-1.67 (0.42)	-2.63 to -0.71	0.003
Fat-free mass (kg)	11	43.02 (1.26)	-0.43 (0.53)	-1.64 to 0.77	0.435
Fat mass (kg)	11	19.59 (2.57)	-1.26 (0.38)	-2.13 to -0.39	0.010
Fat mass (%)	11	29.13 (1.90)	-1.28 (0.69)	-2.83 to 0.28	0.100
Energetic outcomes					
Total energy expenditure (MJ/d)	9	18.92 (0.54)	.	.	.
Activity-related energy expenditure (MJ/d)	9	10.78 (0.32)	.	.	.
Resting metabolic rate (MJ/d)	10	6.25 (0.29)	0.15 (0.19)	-0.27 to 0.58	0.274
Estimated energy intakes (MJ/d)	10	13.00 (1.86)	.	.	.
Accelerometer-related physical activities					
Light accelerations-related activities (h/day)	10	6.13 (0.22)	4.82 (0.30)	4.15 to 5.49	<0.001
Moderate accelerations-related activities (h/day)	10	2.14 (0.23)	0.73 (0.32)	0.01 to 1.45	0.047
Vigorous accelerations-related activities (h/day)	10	0.02 (0.02)	-0.08 (0.02)	-0.14 to -0.03	0.008
Sedentary behavior (% of daily activities)	10	59.52 (1.29)	-23.28 (1.98)	-27.73 to -18.87	<0.001

Values are LS means (SE).

Skin temperature and salivary cortisol during the expedition

Mean daily ambient temperature during the expedition was -17.38°C (range from -26.5 to -11.64 °C) with minimum temperatures reaching up to -31.10°C. Daily skin temperature measured on the chest slightly rose from 36.16 °C (SE 0.12) to 36.36 °C (0.12) (*P*=0.03) (**Figure 3**).

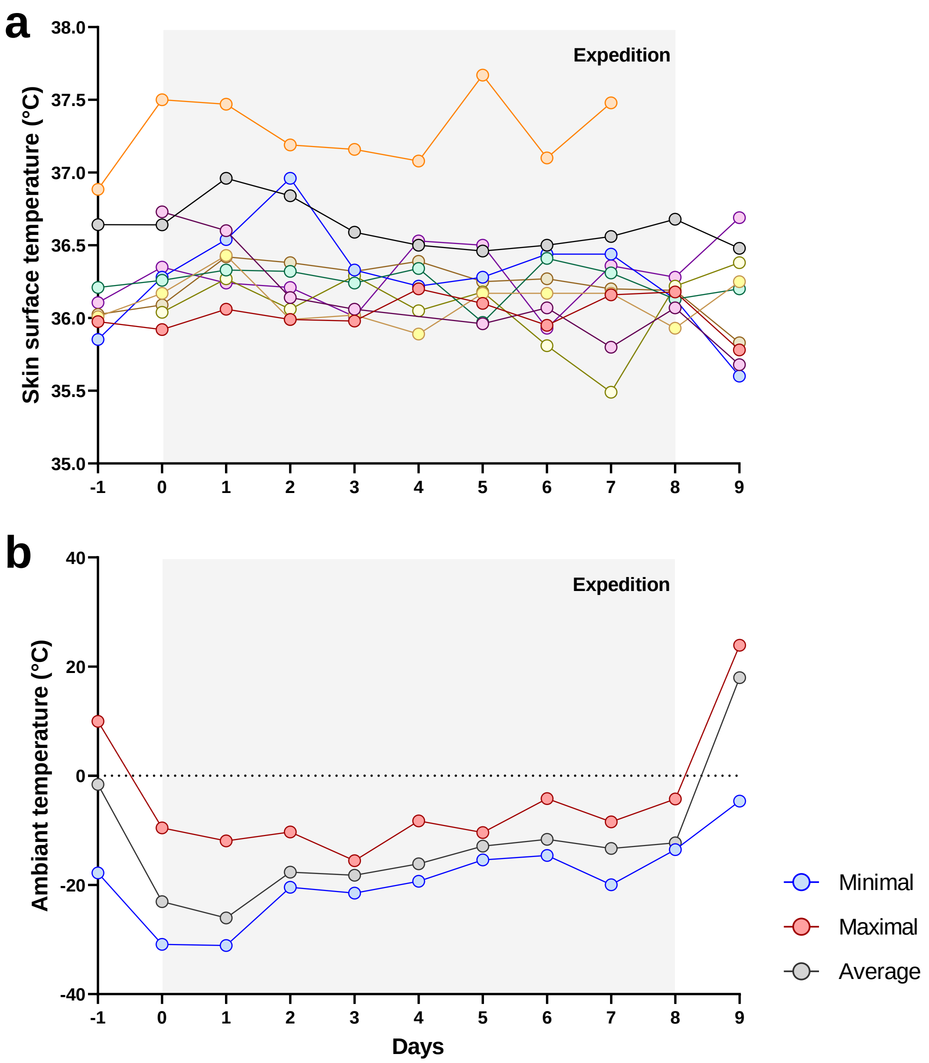

Figure 3: Evolution of individual skin surface temperature (a) and ambient temperature (b) before, during the expedition (shaded area) and after the expedition.

Mean salivary cortisol concentration was not different at the end of the expedition compared to the day before starting the expedition (0.72 µg/dL [SE 0.13] the day before the expedition vs 0.63 µg/dL [0.13] the last day of the expedition, respectively; estimated difference 0.09 µg/dL [0.08], 95% CI -0.27 to 0.09). This suggests that stress level did not change throughout the expedition. Nevertheless, a wide inter-individual variability was observed with salivary concentration ranging from 0.19 to 1.69 µg/dL at baseline and 0.27 to 1.43 µg/dL at the end of the expedition (**Figure 4**).

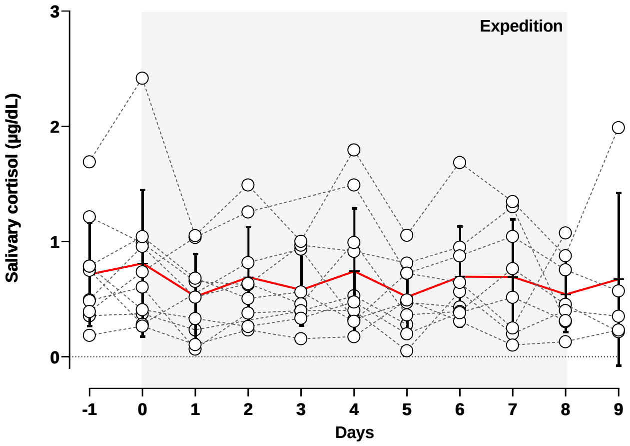

Figure 4: Evolution of salivary cortisol concentration (µg/dL) before, during the expedition (shaded area) and after the expedition. Individual values are plotted with daily means and standard deviation (red line).

Discussion

The POWER study aimed to assess for the very first-time energy requirements of non-athlete and novice explorer women during an autonomous expedition to reach the North Pole. Very high energy turnover rates were measured during the 7-day expedition with a TEE of 18.66 MJ/d, almost 60% being explained by AEE (10.76 MJ/d). This was associated with an average of 8.2 hours per day spent in light-to-moderate accelerations-related activities and a PAL of 3.1. Body mass decreased by 2.42% compared to baseline values, mostly explained by FM loss (-6.45% from initial values). This indicated an energy deficit and that energy intakes were insufficient to cover these high energy needs.

TEE measured in our participants is likely slightly underestimated given that the first 24-hour following the dose ingestion included a day in Longyearbyen to finalize the preparation of the material and rest for a few hours at the hotel, then a 2-hour flight from Longyearbyen to Camp Barneo that took off around 1am followed by a helicopter ride and during which the participants remained seated. They started skiing immediately after the launch of the aircraft. Such high TEE were measured during prior polar expeditions with values ranging from 22 to 27 MJ/d; the differences were likely associated with the conditions of the event, i.e. duration, sledge’s mass, ambient temperature, terrain, environment, etc., and the body mass and composition of the subjects (Halsey & Stroud, 2012; Hattersley et al., 2020; Hoyt et al., 2001; Stroud et al., 1997). In comparison, these TEE were similar than those measured in elite athletes during extreme endurance events such as the Tour de France on cycling

(Westerterp et al., 1986) or the Race Across USA by running (Thurber et al., 2019). Since these high levels are reached and maintained over several days, the concern is more about the match between TEE and EI, especially when the latter is limited (Charlot, 2021; Halsey & Stroud, 2012). We noted a loss of body and fat mass in our participants indicating either that food rations were not sufficient to fulfill the requirements, or that participants were not able to eat enough food to cover their expenses. The estimated energy deficit during the present expedition (i.e. -5.7 MJ/d) was similar to those previously reported during field military training (Johnson et al., 2018; Jones et al., 1993). Of note, these previous studies conducted in military populations during polar-field training camps reported a spontaneous decrease in EI. This volitional reduction in EI has been partly explained by the willingness to spare food items in the prevision of prolonged events duration or the inability to refuel during the mission, but also the lack of palatability along with poor taste and smell of dehydrated food rations (Ahmed et al., 2020). Previous cross-sectional studies observed in the general population an incapacity to consume a sufficient amount of food when PAL values were above 2.2-2.5 (Melzer et al., 2005; Thurber et al., 2019). The present PAL of 3.1 in this novice explorer population may thus partly be at the origin of the negative energy balance observed. However, the design of the study did not allow to accurately track food intakes, and appetite sensation were not recorded during the expedition. Another hypothesis is about the anorexigenic effect of stress (Rabasa & Dickson, 2016) that participants experienced during the expedition. The salivary cortisol concentration used as a proxy of physiological stress level remained stable throughout the expedition, suggesting no increase in physiological stress during the expedition. In addition, no association was found between TEE, RMR or estimated EI and cortisol concentration (data not shown). This being said the first salivary sample was collected the day before the expedition when participants were finalizing the preparation of the material, which was already stressful. Therefore, the pre-expedition sample likely did not represent a true baseline.

The POWER study used 3D-accelerometers to assess daily physical activity pattern showing that light accelerations-related physical activities were the major component of daily physical activities. of note, in a polar environment, light accelerations-derived physical activities are not necessary associated with light-intensity physical activities, i.e. activities associated with low levels of oxygen consumption (1.5-2.99 MET). The accidental and difficult terrain, the altered mechanical efficiency induced by the cumbersome polar suits (Teitlebaum & Goldman, 1972) or the additional energetic cost to sledge the packages (around 50 kg in the present study) by ski (Saibene et al., 1989) slow down the progression of the team and therefore increase the activities detected with light acceleration. However, the efforts displayed by the team members to overcome those challenges are not associated with low energy expenditures as indicated by the very high levels of AEE and TEE measured in our participants. Other factors that we did not measure but are known to influence TEE are shivering and non-shivering mechanisms for thermoregulation (Yurkevicius et al., 2022). It would however be interesting to know the respective impact of physical activities, thermoregulation, stress, disturbed sleep due to the bear watch rotations at night, permanent daylight and other factors on TEE during events in such extreme environments.

Although the POWER study is one of the rare studies investigating energy balance regulation in non-athlete female participants during a polar expedition using gold standard methods including doubly labelled water method, indirect calorimetry, 3D-acceleromteter and impedancemetry, limitations need to be acknowledged. The pre-expedition period was likely not representative of a “true” baseline period. Habitual stress levels, physical activities, and TEE were not measured and energy intake during the expedition was only estimated. Although we measured skin temperature at the chest level before and during the whole period of the expedition, this was a poor proxy of thermoregulation.

Conclusion

Polar expedition represents a major energy challenge, especially for individuals who are neither specifically trained nor acclimated to extreme cold weather. Non-athlete women displayed very high levels of TEE during a 7-day expedition to reach the North Pole in full autonomy and the reached PALs were similar to what is seen during some of the top sportive events. However, environmental and logistical constraints did not allow participants to cover their energy requirements and significant FM loss were observed. If this loss is sustainable for short periods of time, they could have dramatic consequences over prolonged period. These observations emphasize the difficulty for non-professional participants to maintain energy balance during such expeditions, hence the need to optimize food intake in regard to the elevated energy requirements of polar expedition. In a more theoretical perspective, it also questions the limit of regulation of energy balance.

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Discussion générale

Since the beginning of mankind, humans are driven by political, military, sportive or personal motivations to explore new horizons. A large number of these journeys have been taken in harsh conditions and hostile environments. Another major challenge of these explorations and expeditions has been ensuring the adequate nutritional needs of the crews. Nutrition was most of the time inadequate to cover the energy needs, thus leading to energy deficit. While an energy deficit can be sustainable for short periods of time, it will lead to adverse health consequences over prolonged periods. Maintaining a stable energy balance is nowadays considered a central component of the success of missions in extreme environments, as those planned for the next phase of the space exploration (e.g. Moon colonization and Mars conquest) or for the exploration of extreme remoted areas on Earth (e.g. polar regions, oceans, deserts, high mountains, jungles). In this context, this thesis aimed to better understand the regulation of energy balance in humans exposed to extreme environments. Here we focused on space and the Artic. By combining studies conducted in space, on Earth using the bedrest space analog model, and during a polar expedition, this thesis further studied the regulation of energy balance across a wide spectrum of physical activity (PA) in healthy humans.

As hypothesized, we showed that PA is the major determinant of total daily energy expenditure (TDEE) via modifications of PA-induced energy expenditure (PAEE). This indicates that PA is a key factor in the regulation of energy balance. Results from studies on contrasted PA levels and contrasted PA patterns, i.e. contrasted proportion of time spent in different types of PA, showed that all components of PA, i.e. both exercise and non-exercise PA, should be considered when investigating energy balance regulation. PA involves any bodily movements produced by skeletal muscles that expends energy above RMR. Exercise is a subcategory of PA, defined as planned, structured and repetitive PA aiming to improve or maintain one or more components of physical fitness (Caspersen et al., 1985). As shown in the POWER and ENERGY studies, high levels of PA are associated with a mismatch between TDEE and EI. While MNX suggests that EI can be adjusted to very low levels of PA, this was true in the conditions of the study, i.e. with EI being prescribed to cover the energy needs and leftovers being accepted and not with food being presented *ad libitum*. The astronauts who had lower TDEE in space compared to baseline due to lower levels of PA were not able to spontaneously reduce EI enough to match the lower energy needs and were in positive energy balance. Altogether these data suggest that an energy imbalance is occurring at very low or high levels of PA, suggesting that PA and/or PAEE influences the matching between TDEE and EI and hence, the regulation of energy balance.

In this discussion, we will discuss how data from this work are helping better understanding (1) the regulation and control of energy balance during long-term spaceflights and thus better preparing future exploratory missions, (2) the energetic challenges of expeditions in polar regions, (3) the role of physical activity in the regulation of body weight, and (4) the limits of the homeostatic regulation of energy balance.

Some sections of the discussion are adapted from a review published in Obesity Reviews in 2022.

Bourdier P, Simon C, Bessesen D, Blanc S & Bergouignan A. Role of physical activity in the regulation of body weight: Time to consider light physical activity and sedentary behaviors (2022). 24(2): e13258. Obes Rev.

1. The maintenance of energy balance for operational constraints

1.1. Space missions

1.1.1.The exercise countermeasure

Exercise is widely implemented in astronauts daily routine (Hackney et al., 2015; Loehr et al., 2015; Petersen et al., 2016) and has shown beneficial effects on the maintenance of musculoskeletal (Comfort et al., 2021; English et al., 2020) and cardiovascular (Moore et al., 2014; Moore et al., 2015) systems during long duration spaceflights. However, very few studies provided detailed information about the exercise training actually performed by astronauts inflight (Hughson et al., 2016; Trappe et al., 2009). While general space agencies prescriptions state that 2.5 hours are daily allocated to exercise, half of this schedule is actually dedicated to device setting, data transfer and hygiene. In addition, training modalities are usually based on the frequency, duration and intensity of the exercise sessions, but previous studies only presented time spent using the aerobic device or the number of repetitions on the resistive device. This lack of data limits the ability to accurately estimate the exercise-induced energy expenditure but also the optimization of the exercise countermeasure in terms of type, duration, intensity and frequency. The ENERGY study was the very first study to detail workload, i.e. the product between time and exercise intensity, for the three devices currently used onboard the ISS (Bourdier et al., 2022b).

Results from the ENERGY study showed that high volumes of both aerobic and resistive exercise were sufficient to prevent spaceflight-induced fat-free mass loss. However, they induced a concomitant fat mass loss despite the absence of change in TDEE between inflight and on the ground values (Bourdier et al., 2022b). Similar results have been previously reported during bedrest studies with concomitant training combining aerobic and resistive exercise (Bergouignan et al., 2010). In contrast, training associated with low energy cost did not impact fat mass, but did not prevent disuse fat-free mass loss as observed in the least active astronauts from the ENERGY study (Bourdier et al., 2022b) and in the MNX bedrest study. Since only aerobic workload was different between both groups of astronauts in the ENERGY study, it has been suggested that space agencies should refine the terms of exercise (i.e. type, duration, frequency, intensity, pattern) to optimize the exercise prescriptions and benefit most of the physiological systems without adversely affecting of others. This is particularly true given that exercise-induced energy expenditure will determine energy requirements, but also influences the coupling between EI and TDEE and thus the regulation of energy balance.

1.1.2.The space food system

The accurate estimation of energy requirements is a major concern for long-term space missions, especially in the perspective of the foreseen deep-space exploratory for which food supply will be limited (Tang et al., 2021). In addition to the questions raised about food safety, usability, variety, stability and other factors to consider to ensure an adequate food system in space (Cooper et al., 2011; Douglas et al., 2020), the capacity to consume a sufficient amount of energy *per se* requires specific considerations. Despite adequate food supplies onboard, astronauts only consume 80-85 % of the energy intake prescriptions that are based on estimated energy needs (Smith et al., 2005b; Zwart et al., 2014). This incapacity to meet energy requirements in microgravity was linked to a “space anorexia” which may at least partly be explained by disturbed circadian rhythms (the dark / light cycles are of 90 min onboard the ISS), an altered gastro-intestinal tract and a lack of food attractiveness (food palatability, altered taste / smell, spacecraft environment) (Cena et al., 2003; Da Silva et al., 2002; Taylor et al., 2020; Varma et al., 2000). Changes in gut hormones also seem to be at play. Previous data from simulated and actual microgravity reported an increase in the anorexigenic leptin hormone (Blanc et al., 2000). This increased leptin concentration may be partially explained by the spacecraft environment, i.e. alternance of 90-min dark / light cycles and higher body temperature than on Earth (Laurens et al., 2019; Simon et al., 1998; Stahn et al., 2017). However, no change was observed in fasting plasma ghrelin, PYY, and leptin during a 60-day bedrest combined with an aerobic + resistive exercise countermeasure. Of note, fasting leptin concentrations at the end of the bedrest adjusted for fat mass changes were negatively correlated with spontaneous EI (Bergouignan et al., 2010), suggesting it may be an index of EI.

Taken altogether, these results may explain why the astronauts from the ENERGY study who maintained their TDEE close to preflight values lost fat mass despite food supply being sufficient onboard the ISS (Bourdier et al., 2022b). Similar results were observed during bedrest study where EI were not sufficient to match the higher energy requirements induced by a combined aerobic and resistive exercise training, resulting in negative energy balance (Bergouignan et al., 2010). Conversely, the reduction in EI observed in the least active astronauts was expected as their TDEE was reduced by about 20%, due to a decrease in PAEE. However, despite EI only representing 75% of the dietary recommendations, the astronauts who decreased TDEE during spaceflight compared to ground values were still in positive energy and fat balance. These findings are in line with those from the MNX bedrest study, where participants in both control and RVE training treatment spontaneously decreased their EI to match the physical inactivity-induced lower TDEE, with few leftovers compared to theoretical energy needs estimated by space agencies. These findings support the importance to consider each component of both TDEE and EI to optimize the control of energy balance.

1.1.3.How to improve energy balance during long-term spaceflight?

In 1999, Stein et al. proposed an equation to estimate energy requirements during space missions by specifically taking into account the cost of exercise, where $\mathrm{energy\ needs} = \mathrm{a}\ \times \mathrm{RMR} + \mathrm{exercise} + \mathrm{EVA\ activity}$ (a being the activity factor, RMR the resting metabolic rate and exercise and EVA activity the cost of exercise countermeasure and extra-vehicular activities, respectively) (Stein et al., 1999b). Of note, the use of this equation implies to accurately estimate the energy cost of the different activities and exercise performed in the station as well as the EVA. As an example, it was previously shown that running mechanic efficiency was altered on T2 treadmill with EE being higher than the ground-based predictions likely because the bungee ropes used to pull the astronaut on the device induced extra physical work (Convertino, 1990). Future studies will need to determine the specific exercise-induced energy expenditure for each device but also of the non-exercise activities to refine the individual estimation of PAEE in almost real-time.

To date, it was commonly accepted that daily PA in space was essentially restricted to exercise training and was therefore much lower in space compared to ground conditions. However, results from ENERGY showed that total overall daily PA did not change inflight compared to the ground data, especially because of a change in PA pattern. Although ambulatory activities (walking + running) were almost suppressed inflight, they were compensated by an increase in non-ambulatory activities, that are all the other activities detected by the accelerometer. However, time spent exercising on ARED and CEVIS devices only partially explained time spent in non-ambulatory activities, suggesting that something other accounts for total non-ambulatory activities, hence daily PA. The understanding of this “black box” will help to better characterize astronauts’ daily energy expenditures and optimize individual prescriptions since each astronaut will have specific characteristics (e.g. sex, body composition, physical fitness) and tasks during the mission, including intra- and extra-vehicular activities. Briefly, this suggests that methodological developments are needed to improve PA pattern recognition in space and adapt exercise prescriptions *in situ* based on astronauts' spontaneous PA and mission-related PA (e.g. moving in the station, maintenance tasks, and extra-vehicular activities).

1.1.4.Future directions to track energy balance status in situ

Taken altogether, our findings stress out how critical it is to consider the complex relationships between the components of energy balance in space with an integrative approach, rather than focusing on TDEE or EI independently. Accurately estimating food intake and PA (and/or TDEE) onboard the ISS is operationally challenging. The measurement of body composition during the mission represents a more feasible alternative to evaluate energy balance status, with fat mass being considered a good proxy of energy balance under microgravity conditions (Zahariev et al., 2005). Nowadays, only body mass is measured using the SLAMMD device (Space Linear Acceleration Mass Measurement Device) during the mission (Zwart et al., 2014). Body composition measurement is restricted to operational medical assessments before and after mission by DEXA. Bio-impedancemetry or medical imagery could be used instead to track real-time body composition changes and adapt prescriptions *in situ* to ensure energy balance, and to protect crew performance and health (Bergouignan et al., 2016). This would require a pre-validation of the technique inflight against the isotopic dilution method that can be used in space as we proved it in ENERGY.

1.2. Adventure in extreme environment

1.2.1.The estimation of energy requirements

As observed during the POWER study, a major concern for adventures in extreme environment is the mismatch between TDEE and EI leading to potential operational and medical alterations (Pasiakos, 2020).

On one hand, extreme environment compels individuals to cope with high energy-demanding tasks (Charlot et al., 2020; Ocobock, 2016; Stroud et al., 1997). Polar regions offer a unique set of challenges and hazards including extreme temperatures, blizzards and difficult terrain due to the ice being always on the move (crevasses and frozen lakes, channels of open water). These environmental constraints challenge mobility and core temperature maintenance. In addition, the polar suits used to prevent heat loss are known to impair mechanical efficiency resulting in higher energy expenditures (Teitlebaum & Goldman, 1972). The stress experienced by the explorers due to the multiple hazards, dangers and risks specific to the Artic along with sleep alterations due to the polar bear watches to prevent attacks at night, constant day light, and stress, can contribute to energy balance dysregulation (Chaput et al., 2023; Rabasa & Dickson, 2016).

On the other hand, food intake is reduced and several factors might be at play. The most common is the insufficient amount of food intake carried out, especially in the context of full-autonomy adventures during which participants have to optimize the weight of their food and journey-related clothes, tents, and other devices resulting in sledges weighting over 100 kg (Charlot, 2021; Hattersley et al., 2019b). Despite prescribed rations to theoretically cover energy requirements, some episodes of volitional sparing have been reported during military training in case of adverse events that would extend the mission duration and/or modify the initial mission plan since no refueling is possible in these remote areas (Ahmed et al., 2019). As described with the food system in space (Cooper et al., 2011), food provided for polar expedition are high-nutrient density and dehydrated meals to optimize the ratio between energy intake and weight carried (Charlot, 2021; Hattersley et al., 2019b). The food palatability and its accessibility in terms of conservation and cooking ability may also contribute to the reduced EI and need to be optimized to preserve energy balance. Finally, stress as experienced during such expeditions is also known to impair EI (Rabasa & Dickson, 2016). The salivary cortisol concentration used as a proxy of physiological stress level in the PWER study remained stable throughout the expedition, suggesting no increase in physiological stress during the expedition. This being said the first salivary sample was collected the day before the expedition when participants were finalizing the preparation of the material, which was already stressful thus not it was not representative of a true baseline. This might explain the lack of association between salivary cortisol concentration and estimated EI.

1.2.2.Benefits of data obtained with extreme models for the general population

Most of the past studies in extreme environments were conducted in elite athletes or well-trained male military. Very few data are available for non-athlete people and none of them specifically targeted female population. Thus, observations only referred to 50% of the general population. However, women are known to display different physiological responses during physical activity, especially because of sex hormones (Wohlgemuth et al., 2021). Among these differences, body composition and substrate metabolism are commonly reported (Boisseau & Isacco, 2022; Cano et al., 2022). Difference in fatigue and recovery during prolonged efforts have also been reported, women displaying lower fatigability during prolonged efforts than men (Besson et al., 2021; Hunter, 2009). It has also been suggested that thermoregulation differed between men and women. However, these differences disappear when participants are matched for age, acclimatization, body size, and fitness level (Notley et al., 2021; Wohlgemuth et al., 2021).

In addition, highly-trained people represent a marginal fraction of the global population thus limiting the generalizability of the results. This limitation is particularly true when considering the efficiency of locomotion in extreme environment or the capacity to cope with hostile environments for which athletes or militaries are trained for. In this context, POWER was innovative as it described the energy metabolism of non-athlete women who participated in an arctic polar expedition. This study can be linked to those organized by the French-Swiss scientific explorer Christian Clot and his scientific collaborators who aim to investigate physiological and behavioral adaptative mechanisms in extreme environment. For example, the 2022-2023 Adaptation Mission-20 involves 10 men and 10 women (aged 25-45) from the general population who are completely novice to the life in extreme conditions. Participants are taking part in four 30-day expeditions in extreme and hostile areas characterized by either hot and dry, hot and humid, cold and dry, or cold and humid climates. They undergo series of tests aiming to describe their cognitive adaptative capacities and testing for potential sex differences.

In a more general perspective, studying the physiological responses to extreme environment can be an interesting model to approach the limit of human acclimatization, and improve our understanding of specific illness and / or treatments for patients (Grocott, 2008). As an example, the Expedition 5300 aimed to investigate the effects of permanent life at high altitude and hypoxia on blood parameters since several highlanders residing in La Riconada, Peru (alt. 5100-5300 m, highest city in the world) are living with chronic mountain sickness, with values considered to be pathological for lowlander (Stauffer et al., 2020). Another example is the use of space science related research to inform the pathophysiology of accelerated aging, sedentary behaviors and physical inactivity that are major risk factors for chronic diseases including obesity, type 2 diabetes, metabolic syndrome and cardiovascular diseases (Bergouignan et al., 2011). Indeed, these extreme conditions hastens the development of metabolic disorders that usually appear over several years under free-living conditions. Since research in space environment is very restricted because of operational constraints, ground-based bedrest analog models are commonly used to investigate the effects of simulated microgravity (Pavy-Le Traon et al., 2007). Our research group recently combined data from bedrest studies during which different exercise countermeasures were tested, i.e. aerobic and / or resistive, and showed that being physically active (i.e. reach current physical activity recommendations of 150–300 min of moderate to vigorous or 75–150 min of vigorous PA (Bull et al., 2020)) is not necessarily sufficient to counteract all the deleterious health effects of sedentary behaviors (i.e. too much sitting time). In other words, some adverse health effects of sedentary behaviors are likely independent of those from exercise (Le Roux et al., 2021). These conclusions are particularly relevant in a context where the promotion exercise or other spontaneous activities (also called non-exercise activities or light physical activity – LPA) is required to increase daily PA in addition to the reduction of time spent in sedentary behaviors to prevent the development of non-communicable diseases (Booth et al., 2017; Katzmarzyk et al., 2022).

2. The regulation of body weight in extreme environment: inference on the role of physical activity in obesity management

Although obesity is a complex multifactorial disease, weight gain can only result from chronic positive energy balance, *i.e.* calorie consumption greater than energy needs. The causes of this imbalance however remain unclear. Over the past few years, a debate has been growing in the scientific community and the media on the relative contribution of increased energy EI *vs* reduced EE to the obesity epidemic. While the importance of PA in weight management is generally accepted, the role of PA in weight gain is more controversial (Blair et al., 2013; Fisher et al., 2013; Hill & Peters, 2013; Luke & Cooper, 2013; Luke & Cooper, 2014; Swinburn, 2013; Wareham & Brage, 2014). Some investigators promote a diet-centric view according to which the global obesity epidemic observed over the past decades is due to increases in EI rather than to declines in EE due to a fall in habitual levels of PA. Alternatively, Rowland proposed the “activity-stat” concept in 1998 in which TDEE is homeostatically regulated, i.e.., controlled around a fixed value (Rowland, 1998). Pontzer et al. recently proposed that TDEE is rather constrained. According to this theory, while EE increases with PA at low activity levels, it plateaus at higher activity levels as the body adapts to maintain TDEE within a narrow range. High activity levels may be offset by decreases in the other components of TDEE including RMR (the minimal amount of energy required to ensure vital functions) and diet-induced thermogenesis (the energy required to assimilate and store energy after a meal) (Pontzer, 2015). This model has been used to explain why increased levels of PA often have little impact on weight-loss strategies (about 1-2kg) (Foright et al., 2018). While the role of PA in the treatment of obesity is controversial, its benefits for preventing unhealthy weight gain and body weight regain following weight loss is more generally accepted (Melby et al., 2019). In this context, we recently compiled available data from studies that examined the relationships between PA, TDEE, EI and obesity outcomes to address this debate (Bourdier et al., 2022a).

2.1. Physical activity and body weight

Interventional and observational studies observed that clinically relevant weight loss can be achieved if moderate-to-vigorous PA (MVPA) training is above PA recommendations, daily practiced and/or performed under supervision (Donnelly et al., 2003; Swift et al., 2014; Swift et al., 2018).

In the Midwest Exercise Trial (MET) 2, adults with overweight or obesity lost on average 5% of their initial body weight following a 10-month training program with an EE of 1.67-2.51 MJ (400-600 kcal) per supervised exercise session 5 times a week (Donnelly et al., 2013; Herrmann et al., 2015). Similar conclusions were made in the ENERGY study where the most active astronauts, by a combination of high exercise and daily PA, lost fat mass loss while opposite changes were observed in the least active astronauts (i.e. fat mass gain) (Bourdier et al., 2022b). In the Step-Up study, an 18-month behavioral weight loss intervention that combined calorie restriction and PA in adults with overweight or obesity, the individuals who lost more than 10% of initial body weight spent more time in prolonged bouts (>10 min) of both MVPA and LPA than those who lost less than 10% of initial body weight (Jakicic et al., 2014). The E-MECHANIC study further showed that low levels of habitual moderate-to-vigorous PA (MVPA, defined as PA with an EE > 3 METs) (Ainsworth et al., 2000) and activity-related energy expenditure were associated with lower weight loss during a 24-week exercise intervention in adults with overweight or obesity (Höchsmann et al., 2020). Furthermore, while interventions based on low volumes of exercise training did not produce much weight loss (Church et al., 2010; Church et al., 2007; Slentz et al., 2004), training above the current PA recommendations (225-420 min/week of exercise or MVPA) have shown more success (Donnelly et al., 2009). However, other studies showed that high volume of additional PA can induce concomitant decreases in non-exercise PA and increases in sedentary behaviors (SB), especially in people with overweight or obesity (Lefai et al., 2017; Melanson et al., 2013; Riou et al., 2019) and low levels of habitual PA (Höchsmann et al., 2020).

The commonly observed compensatory decreases in LPA in response to high volumes of MVPA may result from the difficulty that sedentary-inactive people encounter when performing unusual and/or new activities of moderate-to-vigorous intensity. For those individuals, increasing LPA may be a reasonable alternative to increase total PA time (Villablanca et al., 2015). Because LPA represents the most variable component of TDEE (Levine, 2003), it has the potential to influence energy balance and hence, body and fat mass. For example, the study from Holliday et al. compared the effect of two interventions: one targeting LPA through increases in daily PA and another targeting MVPA (5 sessions per week of 30 min/day) (Holliday et al., 2018). The first intervention promoting participation in daily life activities resulted in higher daily time spent in LPA, lower sedentary time and greater android fat loss after 24 weeks compared to what was observed in the group assigned to the structured MVPA program. Of note, while the time spent in PA of different activities varied between the two groups at the end of the intervention, the total daily active time was not different. In agreement with observation from the MNX and ENERGY studies, the study of Holliday et al. supports the promotion of activities of daily living as an efficient strategy to increase total PA, reduce body mass and improve adiposity. More recently, Swift et al. observed that the combination of an aerobic exercise protocol with increases in daily steps (to avoid sedentariness) in adults with obesity was more effective than a protocol based on aerobic exercise alone in decreasing waist circumference (-4.7 vs -2.1 cm, respectively), body weight (-4.1kg or -3.5% vs -1.7kg or -1.8%, respectively) and fat mass (-4.7 vs -2.6%) (Swift et al., 2021). Based on these current findings, promoting LPA to decrease sedentariness can be considered a promising strategy to promote weight loss in physically inactive people with overweight or obesity.

2.2. Effect of changes in physical activities on total daily energy expenditure

While an increase in PA should theoretically lead to an increase in TDEE, spontaneous behavioral and physiological compensatory mechanisms seem to be recruited when PA increases (King et al., 2007; Melanson, 2017; Pontzer, 2015; Rowland, 1998). We recently summarized a non-exhaustive list of studies during which free-living TDEE was assessed with the doubly labelled water method before and after an exercise protocol intervention (Bourdier et al., 2022a). Overall, currently available data show a great deal of heterogeneity. While some studies observed an increase in TDEE after an exercise intervention (Herrmann et al., 2015), others did not (Goran & Poehlman, 1992; Hunter et al., 2015; Wang et al., 2017). For example, the MET 2 study conducted in adults with overweight or obesity reported increases of 1.30 MJ/day (310 kcal/day) in TDEE in responders (body weight loss > 5% from baseline) after 10 months of supervised exercise 5 days/week with a controlled energy expenditure of 1.67 or 2.51 MJ (400 or 600 kcal) per exercise session (8.37 or 1.56 MJ/week – 2,000 or 3,000 kcal/week). Of note, non-responders (body weight loss < 5% from baseline) had higher absolute EI and decreased time spent in non-exercise PA compared to responders (> 5% weight loss) (Herrmann et al., 2015). In a 2-month intervention consisting of moderate intensity aerobic exercise conducted in sedentary men with overweight or obesity, Lefai et al. observed no change in TDEE or PAEE due to a spontaneous decrease in non-training activity-related energy expenditure, associated with reduced time spent in LPA (Lefai et al., 2017). However, in the same study the authors observed a significant increase in both activity and TDEE in sedentary male with normal weight adults after the same 2-month intervention on PA (Lefai et al., 2017). TDEE increased from 10.70 MJ/day at baseline to 12.30 MJ/day (2,556 to 2,938 kcal/day) after the intervention. Whybrow et al. observed that young healthy individuals performing 40 min sessions on stationary bicycle targeting 0.01 MJ/kg (3.3 kcal/kg) of body weight for 16 days increased their TDEE up to 13.70 MJ/day (3,272 kcal/day) through exercise-induced energy expenditure (Whybrow et al., 2008). However, no change in body or fat mass was observed. In this study, subjects compensated for about 30% of the exercise-induced energy deficit by increasing EI, which was similar to the degree of compensation reported by Stubbs et al. (Stubbs et al., 2002). Nevertheless, a high degree of variability in compensation among individuals was reported by the authors.

Altogether, these observation suggest that 1) the modalities of PA training likely influence the propensity to compensate for exercise training-induced energy expenditure, and 2) the impact of increases in PA on TDEE may depend on individual characteristics, such as adiposity, habitual TDEE and PA, age, energy balance status, or training status as recently reviewed (Bourdier et al., 2022a). An important point that remains unknown is whether the behavioral and physiological compensatory mechanisms develop as people put on weight or whether compensations are a “pre-existing” condition as described in the “thrifty gene” theory (Speakman, 2008). In other words, do people accumulate fat mass because they compensate more, or do they compensate more because they have greater adiposity? Future studies will need to address this question to advance the science of obesity and improve preventative and therapeutic strategies of unhealthy weight.

2.3. Effect of changes in physical activity on energy intake

The study of the relationship between PA and food intake is not new. In the 1950s following observations in Bengali workers, the French-American nutritionist Jean Mayer described that EI was closely coupled with energy expenditure at medium to high levels of PA in a “regulated zone”. However, at low levels of PA, the coordinated regulation of appetite and energy balance was altered so that EI exceeded requirements and led to weight gain (Mayer et al., 1956). EI being mediated by appetite signals, various studies suggest a “J-shaped curve” between the whole spectrum of PA (i.e. from very low to very high level) and appetite regulation (Beaulieu et al., 2018; Hill et al., 2012; Mayer et al., 1956). Hedonic and behavioral systems regulating EI may be altered in environments where food is consumed in excess. These dysregulations may overpower biologic systems and amplify the disequilibrium of energy balance (Berthoud, 2011).

The concept of "energy flux", defined as "the magnitude of total energy turnover while maintaining energy balance over periods of weeks to months", can help us better understanding these different observations (Melby et al., 2019). This concept suggests that increasing PA for inactive and sedentary people would allow higher EI to balance higher energy expenditure in a state of high energy flux. When compared with a state of low energy flux, high energy flux may better regulate weight and fat gain and limit weight regain (Foright et al., 2018; Melby et al., 2019). This approach might be more sustainable than decreasing EI to match low PA over prolonged periods of time. However, the way energy is expended should be considered, rather than just TDEE *per se* (Melby et al., 2019). Shook et al. conducted a 1-year follow up in 421 male adults with normal weight (Shook et al., 2015). The authors observed higher weight gain in the least active people compared to their most active counterparts. This was partly explained by an incapacity to reduce EI during the period of reduced PA, potentially due to a failure to generate or respond to satiety signals (Stubbs et al., 2004). These results are in line with observations from the ENERGY study where the least active astronauts were still in positive energy balance and increased fat mass. However, bedrests models such as the WISE or MNX studies observed that healthy participants with normal weight spontaneously reduced their EI to the lower TDEE induced by the study design (i.e. suppressed daily PA) and maintained a stable fat mass throughout the bedrest period, hence stable energy balance. While EI were prescribed by space agencies to cover theoretical energy requirements, very few leftovers were reported suggesting that the coupling with TDEE and EI was maintained at low to very low PAL of 1.2 – 1.45 (for the strict bedrest condition and with and without aerobic + resistive exercise countermeasure, respectively) (Bergouignan et al., 2010). Similar results were observed during the MNX study when participants had a PAL of 1.5. Of note, EI was regularly adapted during the MNX study to ensure fat mass maintenance, hence limiting the interpretations about EI regulation in this study.

On the opposite, moderate to high levels of PA improve homeostatic control of appetite in response to acute disturbances (Prentice & Jebb, 2004). Stubbs et al. observed that being moderately active provided better regulation of food intake than being sedentary following *ad libitum* meal, despite no change in hunger, appetite or weight (Stubbs et al., 2004). Myers et al. reported negative associations between disinhibition and binge eating and both LPA and MVPA (assessed during one week in free-living conditions with accelerometers) in people with overweight or obesity (Myers et al., 2017). They further observed that the most inactive individuals had higher fat mass, and that fat mass was strongly correlated with appetite disorders suggesting a bidirectional relationship between physical inactivity and obesity. Habitual activity seems to further influence the effect of increases in PA on EI. The E-MECHANIC trial that prescribed structured PA of 8 or 20 kcal/kg of body weight per session during a 24-week intervention in adults with overweight or obesity showed that habitual baseline MVPA levels, not the PAEE, predict changes in EI and body weight (Höchsmann et al., 2020). However, models promoting high to very high PA level, i.e. the ENERGY and POWER studies, suggest that this relation is limited above a certain threshold since food intake is not sufficient to cover PA-induced energy requirements, thus promoting negative energy balance.

Despite heterogeneity in protocol modalities (e.g. type of exercise, duration and intensity, chronicity, etc.), it has been suggested that PA would influence food intake through hormones secretion in order to reach the targeted “reference” weight (Stensel et al., 2016). For example, Martins et al. observed an improvement in appetite control following 6 weeks of moderate exercise training in 29 healthy sedentary adults (Martins et al., 2007). King et al. found that the increased fasting hunger following a 12-week exercise protocol in men and women with overweight and obesity was accompanied by increased satiation following a fixed meal, partially explained by an increase in anorexigenic hormones release, such as glucagon-like peptide 1 (GLP1) (King et al., 2009). Flack et al. reported in participants with overweight or obesity that greater reductions in postprandial leptin concentration following a 12-week exercise intervention were associated with lower energy compensation (difference between estimated and actual changes in body composition) (Flack et al., 2020). The authors suggested that reductions in the levels of postprandial leptin indicate an improvement in leptin sensitivity with exercise training which helps controlling food intake. During a two-month bedrest study, a model that induces extreme levels of physical inactivity and sedentariness, our research group observed that lean healthy active women were able to adjust their EI to the very low levels of PA, and that fasting leptin was negatively associated with spontaneous EI, thus also suggesting some relationships between PA, leptin and food intake (Bergouignan et al., 2010). These studies show that the coupling between PA, appetite and EI may be primarily influenced by energy flux, but further investigations are needed to better understand the interaction between PA, food intake control and the regulation of energy balance.

3. The limits of energy balance regulation

An underlying question following the regulation of energy balance in extreme environment is the sustainability of such regulation over contrasted PAL, and prolonged periods of time. More specifically, the use of extreme environmental or pathological conditions raises the question of the existence of minimal and maximal PA thresholds beyond which the coupling between TDEE and EI cannot be maintained.

3.1. Is total daily energy expenditure homeostatically regulated?

The concept of homeostasis developed by Claude Bernard in 1865 states that a physiological function is regulated around a setpoint considered as beneficial for the organism. Like every animal, TDEE will increase above RMR when individual starts moving. Results from the present models using actual or simulated microgravity and polar environment show that the type of activity has different energy cost which may be explained by the intensity, the mechanic efficiency, the environmental conditions, and other factors; the total of each individual activity-related energy expenditure (+RMR and diet-induced thermogenesis) resulting in TDEE. In extreme conditions, some compensatory mechanisms (volitional or physiological) have been described to preserve energy balance during extreme rates of PA or limited food supplies, based on changes in energy allocation budget (Halsey, 2021). This budget is defined as the percentage of TDEE dedicated to exercise-induced energy expenditure, daily PAEE or RMR even after adjusting for body composition changes (Dulloo & Jacquet, 1998; Halsey, 2021; Melanson, 2017; Thurber et al., 2019). However, the term of "budget" implies that resources are limited and may be reallocated according to priority needs *in situ*. Based on this concept, Pontzer assessed the relationship between TDEE and PA (objectively measured with the doubly labelled water method and 3D-accelerometer, respectively). Analyses showed a change point (i.e. the activity level at which the slope of the change-point regression becomes indistinguishable from zero) around 230 counts per minute per day (CPM/day), which was estimated by the authors to an approximate TDEE of 2,600 kcal/day (Pontzer et al., 2016). Using data collected in extreme conditions such as the Tour de France on cycling, the Race cross USA by running, an Antarctic trekking or pregnancy, a maximal sustainable PAL has been estimated around 2.5-3.0 (Thurber et al., 2019). This theoretical threshold was obtained when the exponential relationship between PA (expressed as a multiple of RMR) and time flattens. This plateau implies that compensatory mechanisms are at play to reallocate energy budgets based on energy needs (Pontzer, 2015) (**Figure 11**).

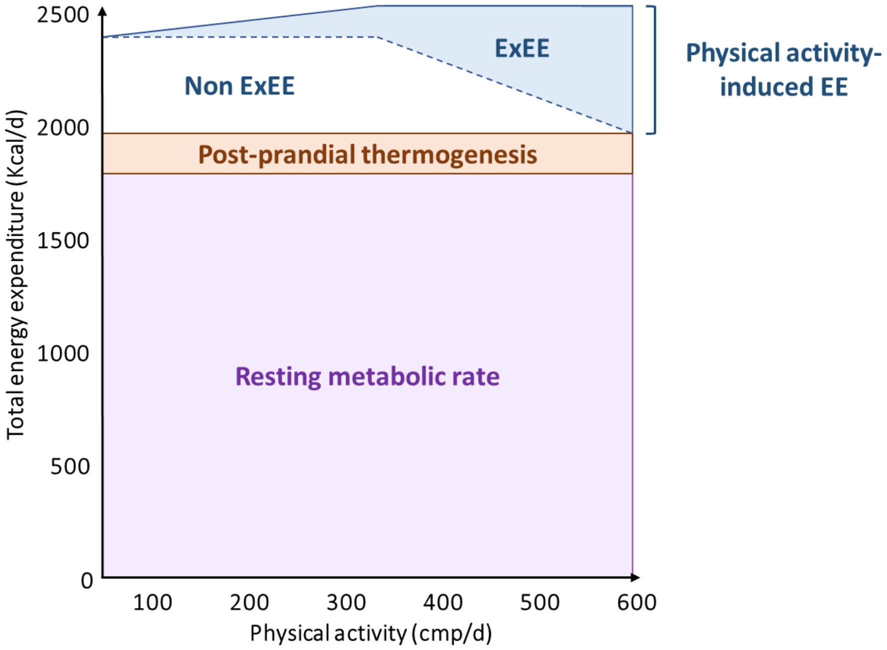

Figure 11: Schematic representation of the constrained model.
Adapted from Pontzer et al. (2016). Data were collected over more than 300 individuals from five population. Total energy expenditure was driven from the doubly labelled water method and physical activity from 3D-accelerometer.
EE= energy expenditure; ExEE= exercise-induced energy expenditure.

While these data remain cross-sectional and conceptual, they can help understanding how individuals can sustain high to very high PA level in extreme environment without being in energy deficit, maintaining body mass and composition around a reference setpoint, or at least in a range of acceptable changes. Similar spontaneous behavioral and physiological compensatory responses can also explain why exercise training elicit lower TDEE and PAEE than the predicted values in sedentary and physically inactive people with overweight (Careau et al., 2021). This can be the result of either spontaneous decreases in non-exercise energy expenditure and/or RMR. As detailed in **paragraph 2.2.**, most studies testing exercise training reported a reduction in non-exercise energy expenditure in response to an increased exercise-induced energy expenditure, leading to TDEE maintenance (Hand et al., 2020; Lefai et al., 2017; Riou et al., 2019).

However, others studies reported stable non-exercise energy expenditure and TDEE in adults with overweight / obesity following a 10-month exercise training (Willis et al., 2020) suggesting decreases in RMR and potentially in DIT (Careau et al., 2021; Halsey, 2021). The point is that this reduction in RMR can occur at the expense of other physiological processes required to maintain homeostasis such as somatic repair or immune response. This has been especially observed in prolonged negative energy balance conditions (Halsey, 2021; Martins et al., 2020; Willis et al., 2022). If this can be acceptable over the short term, somatic maintenance, i.e. the use of energy reserves to fuel the set of processes that keep the organism alive, cannot be compromised over sustained time periods (Sousa et al., 2010). An example of such an energetic trade-off seems to exist between immune response and PA. Indeed, the immune response requires high levels of energy expenditure linked to fever, and may be limited during prolonged periods of high energy turnover (Rauw, 2012). This may explain the post-exercise immune function depression commonly observed in elite athletes, especially when energy is needed to perform high level of PA or repair exercise-induced damages (Gleeson, 2006). However, it is important to keep in mind that the adaptative response of RMR to the increased PA over extended time periods does not find consensus in the scientific literature and requires specific considerations (Halsey, 2021; Thurber et al., 2019; Westerterp et al., 1992). The presence of these energy trade-off tends to confirm the idea of a homeostatic regulation of TDEE around a reference setpoint. Nevertheless, no robust data exist to draw a clear conclusion. Another potential regulatory factor of the maximal threshold of TDEE could be EI given that both components are closely related.

3.2. The capacity to adjust energy intake in response to variation in physical activity, a limiting factor in energy balance regulation

By combining data from our three experimental studies conducted in extreme conditions, i.e. MNX, ENERGY and POWER, we observed a linear relationship between PAL in post-intervention and loss of fat mass in percentage from baseline values (**Figure 12a**). We further showed that fat mass was maintained when participants had a PAL comprised between 1.5 and 2.2. This goes along with previous observations from clinical human studies. Researchers from Leeds in the UK who are one of the world leading groups on the study of energy balance control proposed that a coupling between TDEE and EI exists when PAL is high in the general population in free-living conditions (Beaulieu et al., 2018; Blundell, 2011), i.e. for values between 1.8 and 2.2-2.5 (Melzer et al., 2005). This corresponds to the "regulated zone" described by Jean Mayer in the 1950's (Mayer et al., 1956).

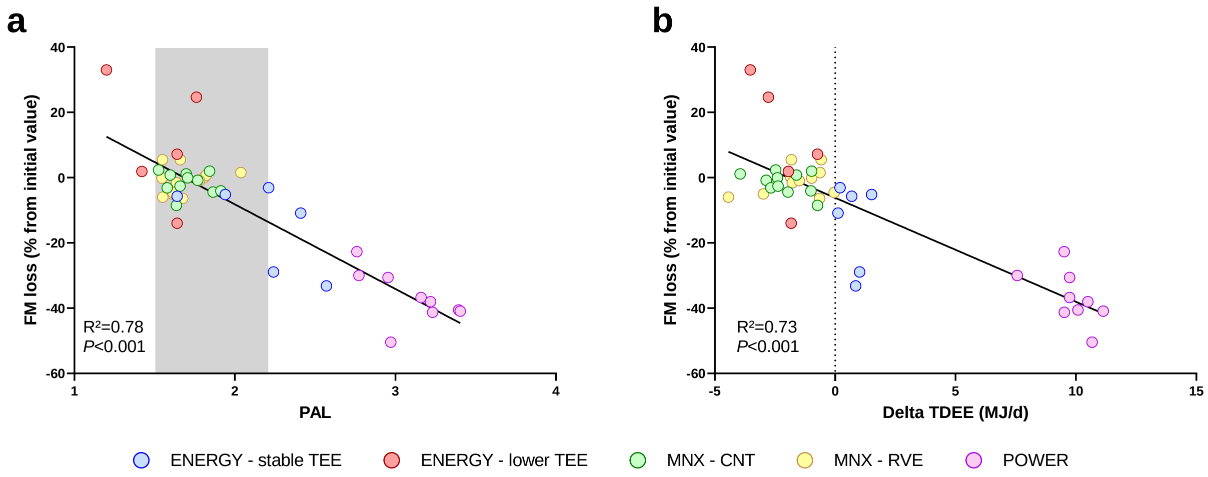

Figure 12: Association between physical activity level (a) or changes in total energy expenditure during the experiment (b) and fat mass changes during the experiment.
a: shaded area represents the theoretical range of PAL where the coupling between EI and TDEE is effective and energy balance is maintained.
TDEE= total daily energy expenditure; PAL= physical activity level; FM= fat mass.
ENERGY= Astronaut's Energy Requirements for Long-Term Space Flight; MNX= Medium duration Nutrition and vibration eXercise; POWER= Physiological adaptatiOns in WomEn during a NoRth Pole expedition.
Stable TDEE= stable TDEE inflight compared to ground-based values; lower TDEE= lower TDEE inflight compared to ground-based values; CNT= strict bedrest treatment (control); RVE= resistive + vibration exercise countermeasure.

Figure 12a also shows that fat mass was gained for PAL below 1.5 indicating that EI was not sufficiently reduced to match the low PAL values. Poor appetite sensations have been commonly observed in physically inactive and sedentary individuals (Myers et al., 2017). However, we observed stable fat mass during the MNX 21-day bedrest study with PAL around 1.2 to 1.5 as well as during the 60-day bedrest WISE study in women (Bergouignan et al., 2010). Altogether, these data suggest that a coupling between TDEE and EI may be possible at low levels of physical activity.

In contrast, participants in our studies elicited fat mass loss when PAL was above 2.2 (**Figure 12a**) which is close to the estimated maximal PAL of 2.5-3.0 that could theoretically be indefinitely sustained without inducing a negative energy balance (Thurber et al., 2019). This threshold was actually found to correspond to an "alimentary limit" equivalent to 2.5*RMR, corresponding to the theoretical maximal quantity of EI that individuals can consume and assimilate. This implies that additional energy requirements over 2.5-3*RMR would require to draw on energy stores to fill requirements, and explains why body mass loss is mostly explained by fat mass loss in response to energy deficit (Raclot & Groscolas, 1995). However, extreme endurance events observed that fat mass, hence energy balance, was maintained at higher PAL values. As an example, studies conducted during the Giro d'Italia and the Tour de France (three-weeks professional cyclist races) observed that body mass and fat mass were maintained throughout the races despite PAL ranging from 4.3 to 5.3 (Plasqui et al., 2019; Westerterp et al., 1986). These observations go along with the model developed by Melzer et al. suggesting that the coupling between EI and TDEE could be maintained until PAL of 4.0-5.0 in highly trained athletes (Melzer et al., 2005). Since energy balance can be maintained in a wide range of PAL, it may be hypothesized that the change in TDEE between free-living baseline condition and the experimental design is more a limiting factor of energy balance (i.e. fat mass loss different from 0) than absolute TDEE *per se* (**Figure 12b**). This hypothesis is supported by previous clinical studies showing that increases in PA do not elicit sufficient increases in EI to cover the energy needs (Thivel et al., 2021). In POWER, we showed that the novice and non-athlete participants did not consume a sufficient amount of food to compensate the unusual and important energy requirements induced by the polar expedition, leading to significant fat mass loss. On the opposite, elite cyclists can adjust their food intake to the high energy needs and maintain energy balance throughout a 3-week race (Plasqui et al., 2019), these high energy rates being commonly experienced during a competitive season. A major difference between both models is that cyclists are highly trained while women from the expedition were non-athletes and novice in extreme environmental expeditions. Of note, it should be acknowledged that participants of the polar trekking had lyophilized food with low palatability in a highly stressful and dangerous environment, while elite cyclists have at their disposal staff dedicated to their health and well-being throughout the race. These observation leads to consider training status, or more generally the adaptability to face high variation in PAL in the regulation of energy balance.

Altogether these data question whether the capacity of an individual to adjust energy balance in response to perturbations of either energy intake or energy expenditure is modifiable. Future studies will need to further investigate the regulation of energy balance but also understand the respective role of the genes, habitual lifestyles, other biological factors and environmental factors in the ability to efficiently and rapidly adjust energy balance in response to acute perturbations.

Perspectives

While it may appear like a trivial concept, the regulation of energy balance actually hides various and complex inter- and intra-components relationships driven by behavioral and physiological mechanisms to ensure a stable body mass and composition. My thesis work opens a few perspectives for future explorations in extreme environment, but also for the general population. These perspectives can be divided into methodological considerations and scientific questions.

The coupling of the doubly labelled water method with indirect calorimetry and PA sensors used in the present studies allowed to determine the components of TDEE. PAEE being the most variable component of TDEE, it is now necessary to i) accurately estimate PA pattern and the time spent in each type of PA (e.g. time spent walking, running, cycling, swimming, and other), and ii) objectively measure the specific energy cost of different types of PA since it varies among individuals and conditions. In the context of future long-term spaceflights, the assessment of PA pattern should be achieved in real time to quickly adapt EI prescriptions *in situ* and thus, avoid major disturbances of energy balance.

Accelerometers are becoming more and more sophisticated with the addition of complementary loggers (e.g. skin temperature or heart rate), and algorithms and activity recognition have been improved with the development of artificial intelligence. However, the estimation of TDEE against the gold standard doubly labelled water method is still based on activities performed in lab settings or free-living common conditions. This implies that further development is needed to extend these equations to extreme environments. Results from the ENERGY and POWER studies clearly highlight this limitation. PA being the main driver of energy balance, its accurate assessment is needed to better understand energy balance regulation and develop adequate strategies to ensure crew integrity through stable body mass and composition during long-term missions in extreme environments. Additional analyses associated with other contributors of TDEE deserve to be investigated such as inflammatory markers or immune status, sleep quality and quantity, and mechanic and / or metabolic efficiency.

On the other side of energy balance, the modulators of food intake and appetite control should be considered too. That means that other factors such as hunger perception, cravings or hedonic sensations, and behavioral operations such as meal timing, or social events should be associated with physiological and metabolic events. Moreover, the acute quantification and qualification of macronutrients would be necessary to track both energy and oxidative (i.e. the balance between macronutrients intake and oxidized) balance. Finally, the association between appetite sensations and gut hormones deserves to be investigated in such models to have a look at the relationships between both physiological and behavioral responses, but also between subjective and objective responses.

As previously discussed, energy balance is regulated over days to weeks. Long-term studies with different stimuli are warranted, e.g. competitive season with repeated short-term events in athletes, or extreme prolonged adventure and sport events, to observe the presence of compensatory mechanisms, the thresholds that trigger them, and potentially the timing and magnitude of their effects. While they remain unpredictable responses, the understanding of mechanisms that determine inter-individual variability will contribute to better understand human physiology. Then, differences among individuals should no longer be set aside the interpretations of results. More importantly, it will lead to the development of individual strategies to optimize the regulation of energy balance. Since all physiological systems acclimatize to local conditions (meaning different from usual daily conditions) to preserve homeostasis in a certain range of normal values, the question of the limits of energy balance regulation in acute and chronic, or sudden and progressive exposure to extreme conditions deserves to be investigated. Finally, the question of the "trainability" of energy balance regulation under various conditions warrants further investigations. Further research should be conducted to test the hypothesis of the limits of energy balance regulation, whether they are biologically fixed or modulable by environmental factors throughout the lifespan. Based on the results from the studies presented in the present manuscript and limitations previously raised, perspectives should hence focus on the following questions:

- What are the intra- and inter-relationships between the components of both energy intakes and total energy expenditure?

Further studies should focus on the interactions between physiological and behavioral responses during stimuli targeting a component or another of the energy balance in individuals with characteristics across contrasted PAL and changes in PAL between usual free-living and experimental conditions. These investigations are important to describe the nature and the direction of the compensatory responses, and better understand their relationships.

- What are the timing and the magnitude of the compensatory mechanisms?

It has been stated that energy balance regulation occurs over days to weeks. However, there is no available data about the threshold or the onset time to trigger the compensatory mechanisms. Similarly, no data exist on their respective contribution to ensure energy balance following various levels of disturbance on one side or another of the balance. Research is needed to experimentally vary different components of the energy balance to investigate the nature and the direction of these relationships. The question of a “dose-response” relationship might be of interest.

- What are the limits of energy balance regulation?

It has been initially hypothesized that energy intakes matched energy requirements in a regulated zone between PAL of 1.5-1.8 and 2.2-2.5. Results from extreme PAL (from bedrest models to professional cyclist races) showed that the coupling between total energy expenditure and energy intake can be expanded to PAL ranging from 1.2 to 4-5. Since all physiological systems acclimatize to current conditions to preserve homeostasis in a certain range of normal values, the question of the limits of energy balance regulation in acute and chronic, or sudden and progressive exposure to extreme conditions should be further studied. The influence of the individual / biological factors, including age, sex, adiposity, training status, and others, should be considered. The notion of acclimatization previously evoked leads to wonder if the limits of energy balance are genetically and/or environmentally determined, or in other words whether the limits of energy balance regulation are fixed or dynamic

Conclusion

La balance énergétique est le résultat d'une régulation fine et dynamique entre les apports et les dépenses énergétiques. Le concept d'homéostasie développé par Claude Bernard en 1865 suggère un maintien de la masse et de la composition corporelle autour d'une valeur de référence considérée comme bénéfique grâce à la mise en place de systèmes compensatoires d'une part et d'autre de la balance énergétique. Si la régulation de cette balance s'adapte aux perturbations légères, les résultats des modèles extrêmes utilisé dans ce travail de thèse montrent les limites de cette régulation en dehors d'un certain niveau d'activité physique, et plus particulièrement lorsque celui-ci varie rapidement par rapport au niveau habituel. Si une dépense énergétique élevée peut être maintenue plus ou moins longtemps selon son intensité, la part des apports alimentaires va devenir le facteur limitant lorsque ceux-ci ne suffisent plus à équilibrer les besoins énergétiques au-delà d'un certain seuil. A l'opposé, la régulation des apports énergétiques serait inefficace lorsque l'inactivité physique et la sédentarité induisent une dépense énergétique trop faible, résultant en une balance énergétique positive et une prise de poids progressive.

Cette incapacité à couvrir les besoins énergétiques via l'alimentation peut s'expliquer par deux mécanismes. Le premier est un manque de stimulus de la prise alimentaire, notamment observée dans les modèles de microgravité (réelle ou simulée) utilisant des contremesures exercice combinant des mesures de type aérobie et résistif. L'autre raison est une incapacité à ingérer la quantité de nourriture suffisante, en raison des limites du système gastro-intestinal comme observé au cours d'évènements sportifs extrêmes tels que les expéditions polaires.

Toutefois, la capacité à maintenir une balance énergétique négative sur le long terme reste encore méconnue notamment en raison de la nature diverse des compensations pouvant être stimulées, mais aussi de la nature du déficit ou encore des caractéristiques individuelles des participants.

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Annexe 1: How interdisciplinary research at the crossroad between socio-cultural anthropology, nutritional and physical activity physiology can help addressing the obesity epidemic

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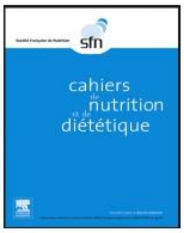

POINT OF VIEW

How interdisciplinary research at the crossroad between socio-cultural anthropology, nutritional and physical activity physiology can help addressing the obesity epidemic

Comment la recherche interdisciplinaire au carrefour de l'anthropologie socioculturelle, de la physiologie nutritionnelle et de l'activité physique peut aider à lutter contre l'épidémie d'obésité

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KEYWORDS
Epidemiological transition;

Summary Despite large global initiatives to manage obesity, its prevalence reaches pandemic levels. A potential reason is that the complex interactions between biological, behavioral, and socio-ecological factors and their respective role in the regulation of body weight (BW) and

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Metabolism;
Anthropology;
Body weight;
Physical activity;
Pre-industrial
populations

fat mass are still not well understood. Our view is that as long as physical activity (PA) is above a certain level, diet, genes and other factors play a role, but their contribution is less pronounced. However, PA levels below a certain threshold uncouple energy intake and energy needs, and impair metabolic control, thus promoting long-term excessive BW and fat mass gain. Technological advances of the past centuries have most likely decreased PA below this threshold in our societies. The epidemiological transition model summarizes the changes in lifestyle, diet and PA that initiated the onset of obesity in Westernized countries. We believe that to identify which factors pose the greatest risk for excessive BW gain, scientists need to study lifestyles, diet, PA and the metabolism of pre-industrial populations, who are undergoing this transition, in a comprehensive metabolic, behavioral and socio-anthropological approach. Here we are presenting the related state-of-the-arts, current gaps in knowledge and future directions.

MOTS CLÉS
Transition
épidémiologique ;
Métabolisme ;
Anthropologie ;
Poids corporel ;
Activité physique ;
Populations
pré-industrielles

Résumé Malgré les programmes de santé publique mis en place à travers le monde, la prévalence de l'obésité atteint des niveaux pandémiques. Une des raisons possibles est que les interactions complexes entre les facteurs biologiques, comportementaux et socio-écologiques, ainsi que leur rôle respectif dans la régulation du poids corporel et de la masse grasse ne sont toujours pas bien compris. Notre groupe de recherche souscrit à l'hypothèse selon laquelle tant que l'activité physique est supérieure à un certain niveau, le rôle de l'alimentation, des gènes et des autres facteurs reste. En revanche, dès que le niveau d'activité physique passe en dessous d'une certaine valeur seuil, les apports énergétiques et les besoins énergétiques sont découplés, et le contrôle métabolique altéré. L'ensemble de ces changements favorise une prise de poids et de masse grasse excessive à long terme. Les progrès technologiques de ces derniers siècles ont très probablement fait baisser l'activité physique en dessous de ce seuil dans nos sociétés occidentales. Le modèle de la transition épidémiologique résume les changements de l'alimentation, de l'activité physique et de la culture ou modes de vie qui ont déclenché l'apparition de l'obésité. Nous pensons que pour identifier les facteurs qui présentent le plus grand risque pour une prise de poids excessive, les scientifiques doivent étudier le métabolisme, l'alimentation, l'activité physique et le mode de vie des populations préindustrielles. Nous présentons ici un modèle de travail expliquant comment les facteurs proximaux et distaux contribuent à une prise de poids, et les lacunes actuelles dans les connaissances et les orientations futures.

Introduction

The pandemic of obesity places tremendous burdens on societies and health care systems [1]. Despite intensive efforts developed across the globe to reduce the prevalence of obesity, all attempted strategies have failed [2]. This may be explained by the fact that how excessive weight gain is affected by biological, environmental, and social factors remains one of the most debated research topics [3,4]. This may be due to the fact that past socio-ecological transitions that initiated excess weight gain related to an excess of fat mass, in our modern industrial societies ended decades ago, and long-term studies in relevant populations are lacking.

The diet, demography, health and physical activity transitions are often reunited in the concept of epidemiological transition, i.e. the change in the pattern of mortality and disease from high children mortality and infectious diseases to chronic diseases. How these transitions impact the social, ecological, biological, behavioral and cultural factors associated with diet and physical activity, and ultimately weight and fat mass regulation, are part of the debate on the etiology of obesity. Rather than being independent we believe the effects of those transitions are progressive and synergistic.

Understanding the respective contribution and synergistic effects of the biological, behavioral and socio-eco-anthropological factors to the global obesity epidemic requires novel approaches. Our interdisciplinary group of research believes that studying pre-industrial populations who are currently facing major socio-ecological transitions will help addressing these challenges. In this viewpoint, we will present the limitations of past traditional research, the gaps in knowledge that need to be addressed and the arguments that support the use of pre-industrial populations for future research.

The obesity pandemic, a complex problem

According to the law of energy conservation, body weight gain can only result from a positive energy balance, i.e. an excess of calories intake over calories expended. If the theoretical principle of energy balance seems trivial [5], its regulation is complex. It involves intertwined genetic, epigenetic, physiological, ecological, social and cultural dimensions [6]. Because the epidemic has mainly occurred over the past 50 years, blaming genetics alone is inappropriate. The regulation of energy stores is a complex and dynamic process influenced by proximal factors, including

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sex, age, genes, aerobic fitness and others, that modify both intake and expenditure. It is also influenced by distal environmental factors at the societal, cultural and global levels, which modify lifestyles and behaviors [6]. The influence of these combined factors triggering weight gain is recapitulated in the notion of diet, demographic and physical activity transitions, all somehow reunited in the epidemiological transition model. This transition includes changes in diet (high-fat and energy dense food), energy expenditure (low physical activity levels), lifestyle (sedentary behaviors, feeding behaviors and job occupations) and culture, which are the primary socio-ecological drivers of the obesity pandemic [7—11].

The key role of physical activity in the regulation of body weight

The role of exercise and physical activity in the regulation of body weight has recently been the topic of animated debates in both the scientific community and the media. Diet-centric research groups argue that the diet transition is essentially responsible for the onset of the obesity epidemic. By contrast, our view is that as long as physical activity is above a certain level, diet, genes and other factors play a role, but their contribution is less preponderant.

In the 1950s, Jean Mayer, a French American nutritionist, suggested that beyond being the most variable component of total energy expenditure (TEE), physical activity is a major determinant of energy intake (see [12]). In addition, below a certain physical activity level (PAL = TEE/RMR, where RMR is resting metabolic rate) threshold (likely around 1.7—1.8) that we have most certainly reached in our modern societies, energy intake, no longer TEE, drives weight regulation. These early findings were later supported by observational and intervention studies [13,14]. More recently, we showed that physical activity energy expenditure (PAEE), but not TEE, predicts nutrient partitioning between oxidation and storage [15]. The effect of physical activity on food intake and metabolism is likely the result of its action on metabolic flexibility, i.e. ability of the body to adjust substrate use to changes in substrate availability and energy demand. The concept of metabolic flexibility implies that health is determined by the ability to adapt to conditions of temporary stress, such as overfeeding, and thus maintain or regain homeostasis. Chronic stress conditions may induce adaptation processes that go beyond the limits of normal metabolic flexibility leading to progressive inflexibility, which in turn contributes to a disease onset. Our view is that inability to maintain this flexibility in an organism as a phenotype appears with insufficient levels of physical activity; this is the metabolically inflexible phenotype.

In support, we showed that physical activity predicts metabolic flexibility [16—18], and that physical inactivity induces an inability to adjust fuel use to match the changing fuel availability and energy demand (i.e. metabolic inflexibility). Metabolic inflexibility precedes the development of glucose intolerance in the pathophysiology of insulin resistance [19]. Importantly, these associations between PAEE and nutrient partitioning and metabolic flexibility were observed independent of changes in energy balance, and even in absence of an increase in TEE [20]. This suggests an independent role of physical activity and PAEE in the regulation of metabolism. In support of this, we recently showed that the inability to both decrease time spent sedentary and adjust fuel use (metabolic inflexibility) in response to an acute overfeeding episode is correlated with long-term weight gain [21,22]. Because of the high occurrence of overfeeding events over a lifetime, these findings are highly relevant. Finally, we believe that the effects of physical activity on metabolic flexibility may contribute to the mismatch between excess body weight and adiposity and the absence of metabolic disorders that is commonly observed in metabolically healthy obese individuals. This is supported by a meta-analysis conducted by Barry et al. [23] showing that regardless of BMI, normal weight unfit individuals have a risk of mortality twice higher than their normal-weight fit counterparts. Furthermore, fit individuals with overweight or obesity had similar mortality risks as normal weight fit individuals.

Taken altogether, this data suggest that physical activity plays a key role in the regulation of energy expenditure, energy intake and metabolic control, which are the main tenants of body weight regulation. Physical activity levels below a certain threshold are associated with a metabolically inflexible phenotype that impairs appetite regulation, energy intake, and metabolic control promoting weight and fat mass gain over the long term. We hypothesize that environmental changes lead to changes in physical activity, diet and lifestyle/culture (Fig. 1):

- during the first phase of the nutrition transition, improvement in food intake, i.e. increase in protein, micro-nutrients and energy intakes, decreases the prevalence of under-nutrition and malnutrition. Healthier food intake improves the ability of the body to adapt to physiological stresses and increases body weight to healthy values, mainly due to increase in fat-free mass. However, sugar, high fat content and salt start to appear in the diet;
- during the physical activity transition, physical activity decreases leading to drops in PAEE (when normalized per kg of body weight) and PAL that reaches a threshold corresponding to a metabolic tipping point. This is associated with an alteration of the regulatory mechanisms of food intake leading to an uncoupling between energy intake and expenditure, and a metabolically inflexible state, which are favoring body weight gain and excessive fat mass accumulation. Metabolically inflexible phenotypes are then more vulnerable to the impact of poor diet but also to the adverse health effects associated with social and cultural changes, which increase the overall disease burden associated with obesity [24]. Other factors influencing body weight and composition regulation such as poor diet (high-fat, high saturated fatty acid, high fructose), increased stress, altered social structures and interactions are therefore appearing;
- with more advanced technology as those present in most developed countries, additional factors such as poor sleep hygiene, endocrine disruptors, high levels of CO_2, etc. will come at play and influence the regulation of metabolism and energy balance.

In summary, as long as sufficient levels of physical activity are maintained, the prevalence of overweight is kept low even in presence of dietary changes. However as soon as physical activity levels drop under a certain threshold and meet the metabolic tipping point, the ''perfect storm'' is in place to trigger and boost the obesity epidemic. We believe that to understand which factors are contributing to the

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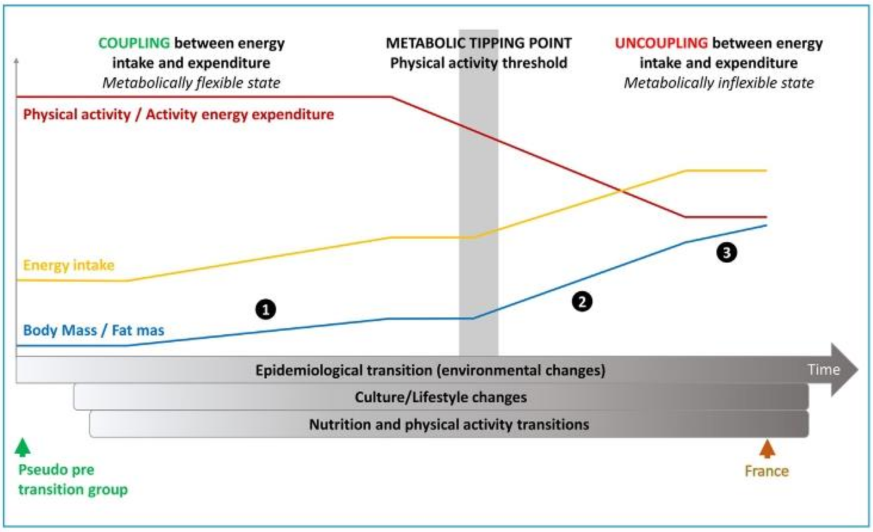

Figure 1. Working model. Simplified illustration of the impact of epidemiological transition induced by environmental changes on cultural/lifestyles, nutrition and physical activity, and on energy intake, physical activity energy expenditure, and body weight and fat mass.

epidemic of obesity, we need to investigate this overall phenomenon. The challenge resides in the available approaches to test this global hypothesis.

What have we learnt so far?

The low prevalence of obesity in most developing countries and pre-industrial populations compared to the high prevalence in Western countries supported the hypothesis that energy expenditure and diet differs between populations at different stages of epidemiological transitions [25]. If the shifts in diet (diet transition) have been well documented, the changes in physical activity (physical activity transition) remain a major gap in our knowledge [4,13]. A commonly shared view is that populations in developing countries must have higher PAEE than industrial societies [26]. Recent meta-analysis compiled studies during which free-living total energy expenditure (TEE) was measured with the gold standard doubly labelled water (DLW) method (see Fig. 2 and Box 1). Unexpectedly, the meta-analysis did not show differences in TEE adjusted for body weight or PAL between low and middle human development index countries [27]. One of the meta-analysis even suggested that PAEE slightly increased in industrial countries whereas PAL remained stable [28] in the 1980s—1990s, a time period during which obesity prevalence increased. While informative, these studies cannot replace longitudinal data. To our knowledge, only the elegant METs study provided longitudinal data on body weight gain and physical activity in five populations spanning different degrees of the epidemiological transition (rural Ghana, USA, urban South Africa, Seychelles, urban Jamaica) [29]. No associations between accelerometry-derived activity at baseline and 2-year BW change were observed [30]. Altogether these findings questioned the role of reduced TEE and physical activity in the onset of body weight gain and have generated animated debates. However, the paucity of data in traditional populations have precluded clear conclusions and fed the debate.

Box 1

- Daily Total energy expenditure (TEE) is defined as the sum of physical activity-related energy expenditure (PAEE), thermic effect of food (TEF — i.e. energy needed to assimilate and store meal-derived energy) and resting metabolic rate (RMR — i.e. the minimal energy required to ensure vital function maintenance).
- Physical activity-related energy expenditure (PAEE) corresponds to energy required to perform exercise (i.e. structured physical activity) and other daily life physical activities.
- Thermic effect of food (TEF) is the amount of energy required to assimilate and store nutrients after a meal.
- Resting metabolic rate (RMR) is the minimal energy needed to maintain vital functions at rest.

Answers to promises and pitfalls of current data depends on methodological issues and interdisciplinary science

A lack of field data. Most previous reports are compilations of existing literature [27,28,31]. In the 1980s, when the DLW method was developed in humans, most industrial countries had already been subjected for multiple decades to the epidemiological transition. Changes in TEE had therefore plateaued and DLW studies were measuring TEE at a new and lower steady state. Similarly, most studies in developing countries compared populations who were already sedentary in a mix of sub-urban/sub-rural environments. Although these data are important, they did not allow to fully detect the changes in the determinants. To address this challenging question, the appropriate scientific approach is to conduct longitudinal studies in populations who have not transitioned from a pre-industrial lifestyle to an urban/modern lifestyle yet.

The regulation of TEE is debated in Westernized populations. Because physical activity is the most variable

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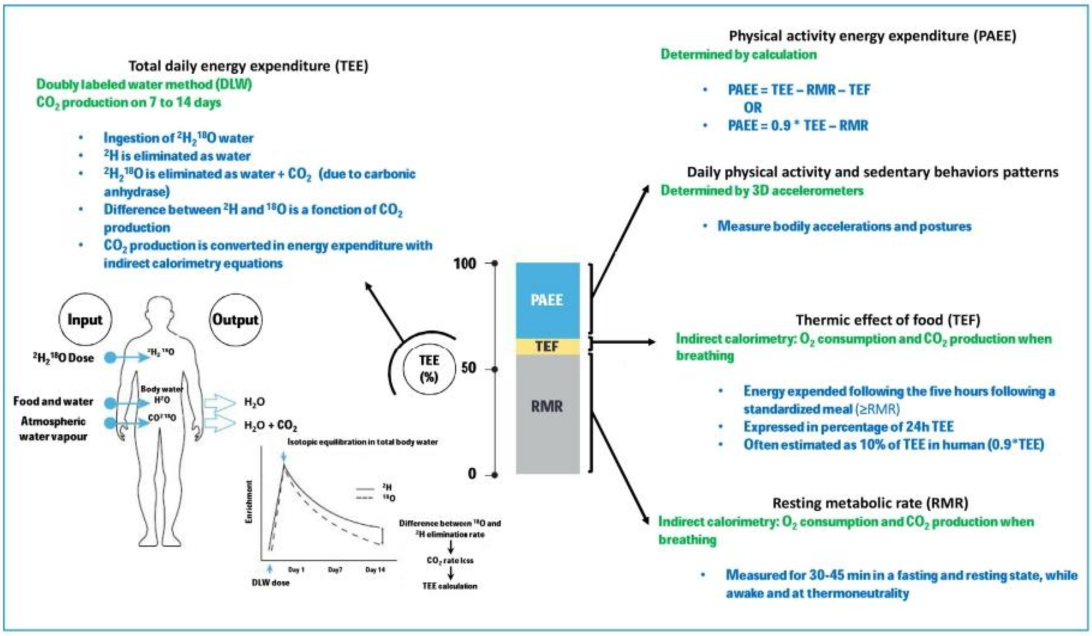

Figure 2. Total energy expenditure and its components: definition and methods. TEE is calculated with the doubly labelled water method (DLW). The subject ingests a $^2H_2{}^{18}O$ dose. Total body water is enriched with stable isotope and urine samples are frequently collected to measure the enrichment of ^2H and ^{18}O. While ^2H is excreted from the body as ^2H_2O, ^{18}O exists the body as both $H_2{}^{18}O$ and $C^{18}O_2$. The difference between ^2H and ^{18}O elimination rate (in blood, saliva or urine samples) corresponds to the production of CO_2 production. By using the classical equations of indirect calorimetry, we can estimate the average daily TEE over the period of measurements (usually between 7 and 14 days). TEF and RMR are measured by indirect calorimetry (measured of CO_2 excretion and O_2 consumption). RMR is measured in fasting state, at thermoneutrality and while the person is awake. TEF is measured for 4-5 hours following a standard meal and corresponds to the increment in energy expenditure above the RMR. TEF can also be estimated as 10% of TEE. PAEE is determined by calculation with the formula PAE =TEE − −RMR − TEF or PAEE = 0.9 × TEE − RMR (if TEF is estimated and not directly measured). Moreover, the pattern of physical activity (i.e. time spent in sedentary activities or light, moderate or vigorous activities) can accurately be recorded with 3D-accelerometers measuring both acceleration and postures. PAEE can further be derived by using validated algorithms.

component of TEE, it is thought that the greater moderate-to-vigorous intensity activity (MVPA) is, the higher is TEE. Pontzer et al. [32,33] recently challenged this simple relationship. Although hunter-gatherers engage in large volume of MVPA, no relationship was found between time spent in MVPA and TEE. They hypothesized that high activity levels are offset by decreases in the other components of TEE, i.e. RMR, thermic effect of food (TEF) or light intensity physical activity (any body movement of daily life including walking, gardening, taking the stairs, doing dish washing, etc.). They proposed the concept of constrained TEE [34], in which TEE increases with physical activity at low levels but plateaus at higher activity levels as the body adapts to maintain TEE within a narrow range. This hypothesis challenges our current knowledge of the regulation of energy balance and warrants further studies. However, Westernized populations are not suited for such studies as they have engineered activity out of daily life. Traditional populations are ideal to test this hypothesis.

The precision of existing data on energetics is disputable. Previous comparative studies measured TEE and its components with relatively low precision and accuracy. DLW-derived TEE requires experimental and analytical precisions to reach 1-2% accuracy and 5-6% precision as obtained in our lab; however large variability existed and still exists across laboratories [35]. Because of the constraints inherent to field conditions, most past studies have estimated, rather than measured, RMR using equations known to have low precisions [36]; and TEF has been assumed to be constant (10% of TEE). With the propagation of errors, the estimation of PAEE (PAEE = TEE-RMR-TEF) has necessarily low precision. This is critical given that a daily energy gap (difference between energy expenditure and intake) not higher than 50-100 kcal/d[37] is thought to be sufficient to induce unhealthy weight gain and excessive fat mass at the population level. Normalization of metabolic rates is another debated topic. For example, Gallagher et al. [38] reported that lower RMR among African-American adults was likely due to lower volume of high metabolically active organs contributing to RMR, which was not accounted for by statistical adjustments. Long-term studies in pre-industrial populations using state-of-the-art techniques are needed to assess TEE and its components with precision achieved in clinical trials. Metabolic rates need to be properly adjusted by including body size, as measured via body surface and volume, and a dissociation between low and high metabolically active organs contributing to RMR.

Physical activity is not a homogenous component. Most past studies assumed that PAEE is a homogeneous compartment of TEE. However, PAEE represents energy expended during the complete 24h-nycthemeral cycle from sleep and sedentary activities to vigorous exercise. Activities differing in intensity and in bouts duration might not have the same effect on energy balance [39]. Others and we have also questioned the impact of daily light-intensity activities [20] and sedentary behavior patterns on weight regulation, independent of MVPA [40]. We further showed that a comprehensive view of the activity/sedentary components is needed to prevent excess weight gain during adolescence, another transition situation [41]. Moreover,

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although the more recent studies used 3D-accelerometry [42,43], the commonly used algorithms overestimate MVPA and do not give precise information on sedentary behaviors, light-intensity activities and posture. Understanding activity behavior in relation with the environmental context also needs information on the location and context where the activity is performed. The phenology of the complete 24 h activity cycle needs to be precisely assessed to understand the effects of the physical activity transition on weight regulation and health [44].

Diet patterns and quality, an unavoidable determinant of energy balance and metabolic health. Improved dietary profile has been associated with reduced BW and healthier metabolic profile [45]. Moreover, beyond its energy and macronutrient composition, a better nutritional quality of the diet has been associated with a lower mortality risk [46,47]. Because food is rarely consumed in isolation, food profile analysis allows to analyze how different food components aggregate together and integrate the synergistic effects of diet as a whole, compared to food items taken in isolation. For this purpose integrative methodologies that consider the whole diet by deriving dietary patterns, data-driven methods such as principal component analysis (PCA) or clustering [48] are needed.

The socio-anthropological dimension, a parameter influencing health. During epidemiological transitions in rural populations, the modernization/urbanization processes impact living conditions and lifestyles that include eating patterns, transhumance patterns and professional/social activities, needing a sociocultural approach to better understand the impact of social background and cultural identities. This complementary approach will allow to detect changes at smaller scales and better understand the socio-cultural dynamics involved in behavioral changes [49]. For instance, the rapid evolution from a traditional rural pastoralist to an urban lifestyle, as observed in other rural populations exposed to urbanization process [50] can disrupt the social structure affecting lifestyle and quality of life, and involving higher social stress level. Precisely, the urban transition affects local dietary and physical activity habits and their associated representations as well as body weight norms [51,52]. Social representations of a population correspond to a form of knowledge, socially elaborated and shared, contributing to the construction of a common reality [52]. They consist as much of knowledge and opinions as of beliefs intended to legitimize behaviors and practices. Rapid changes in the social representations and practices of diet and physical activity are inseparables with structural changes of the society. Clearly, feeding and physical activity must be considered in their complex interactions with the environment, biology, and local socio-cultural norms as developed by Poulain et al. [53] and Drenowski & Poulain [54].

Both poor social relationships [55] and stress [56] caused by a degraded sociocultural environment have been associated with adverse health outcomes. Stress has also been linked to unhealthy behaviors such as poor diet [56]. Given the rapid urbanization process in different rural populations, future research will therefore need to employ a bio-socio-anthropological approach to assess changes in the social representations of body weight and lifestyles related to body weight within the context of rapid sociocultural changes potentially associated with social stress levels and quality of life, and their interactions with energy balance-related determinants will need to be assessed.

Answers reside in populations who have not completed their epidemiological transition

Systemic and holistic studies of pre-industrial populations are needed. In the above reported meta-analyses, data from pre-industrial populations and populations from low to middle income countries were underrepresented. This bias masked a large inter-populations variability in the socio-ecological environments they are living in. Although food availability, social structure, and lifestyles influence diet and physical activity patterns and health, they have been overlooked in previous comparative studies [57]. Yet they differ between pastoralists, agriculturalists, horticulturalists, hunter-gatherers, etc. For example, the ''traditional'' societies in South Africa (38 ± 34 min/d) and Seychelles (38 ± 34 min/d) had much lower levels of MVPA than the Hadza (135 ± 91 min/d), but still greater than their counterparts from the USA (Urban Chicago: 26 ± 32 min/d) [58]. Similarly, non-technology dependent agricultural societies have daily activity levels 3-fold higher than levels shown in hunter-gatherers [59]. On the other side, we showed that consumption of processed energy-dense food was higher in urban Cameroonians compared to rural ones and that valorization of overweight was associated with obesity status [60]. To fully assess the determinants of body weight regulation and metabolic health in relation to the epidemiological transition and the specific impact of physical activity, future research will need to simultaneously consider the anthropo-socio-ecological environment, diet and other lifestyles (e.g. sleep), as well as their interactions.

The need for longitudinal and comparative holistic and systemic studies in traditional populations. For all the reasons mentioned above, we are convinced that only longitudinal studies of populations from pre-industrial countries spanning different phases of the epidemiological transition, including the few remaining traditional populations of agriculturalists, pastoralists and horticulturalists around the world, will improve our understanding of the causes of the obesity epidemic. This is challenging because the populations must be selected based on specific anthropo-socio-ecological parameters that will allow for defining a near-zero time of changes that closely approximates human lifestyles prior to industrialization, as it is impossible to find nowadays a ''true zero time''.

Conclusions

The respective contribution of the different factors associated with the Western lifestyle and known to pose a high risk of obesity remains highly debated. However, diet, physical activity and lifestyle of pre-industrial populations provide the best model to address this challenge. Future research will need to compare these factors in industrial and pre-industrial populations, but also to track the impact of the ongoing transitions on these factors and the associated changes in body weight and metabolic health. Exciting findings are likely to come from this emerging field of research at the crossroad between metabolism, ecology and anthropology.

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Ethics

Not applicable.

Contribution of the authors

PB, CS, SB and AB have drafted the manuscript. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Disclosure of interest

The authors declare that they have no competing interest.

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Annexe 2: Metabolic profile in women differs between high versus low energy spenders during a low intensity exercise on a cycle-desk

scientific reports

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Metabolic profile in women differs between high versus low energy spenders during a low intensity exercise on a cycle-desk

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Active-desks are emerging strategies aiming at reducing sedentary time while working. A large inter-individual variability in energy expenditure (EE) profile has been identified and has to be explored to better optimize and individualize those strategies. Thus the present study aimed at comparing the metabolic and physical profile of individuals characterized as high spenders (H-Spenders) *versus* low spenders (L-Spenders) based on EE during a cycle-desk low intensity exercise. 28 healthy women working in administrative positions were enrolled. Anthropometric, body composition and fasting metabolic profile parameters were assessed. EE was determined by indirect calorimetry, at rest and during a 30-min cycle-desk use. Participants were categorized as H-Spenders and L-Spenders using the median of the difference between EE at rest and during the 30-min exercise. H-Spenders had higher mean EE ($p < 0.001$) and carbohydrate oxidation ($p = 0.009$) during exercise. H-Spenders displayed higher values for fasting plasma insulin ($p = 0.002$) and HOMA-IR ($p = 0.002$) and lower values for HDL-cholesterol ($p = 0.014$) than L-Spenders. The percentage of body fat mass was significantly higher in H-Spenders ($p = 0.034$). Individuals expending more energy during a low intensity cycling exercise presented a less healthy metabolic profile compared with L-Spenders. Future studies will have to explore whether the chronic use of cycle-desks during work time can improve energy profile regarding metabolic parameters.

Over the last century, the technological revolution (i.e. work automation, increase in transports use) led to tremendous changes in human behaviors favoring a global reduction in physical activities (PA) and an increase in sedentary behaviors (SB)[1], particularly in high-income countries[2,3]. The independent and joint effects of those more recently adopted behaviors raise the risks of cardio-metabolic morbidity and all-cause mortality[2,4]. With the growth of desk-bound activities in the work environment, SB have taken an important part in individuals' daily time[5] resulting in a reduction in PA and total energy expenditure (EE)[6]. Active workstations (sit-to-stand, treadmill or cycle-desks) have been suggested as potential solutions to counterbalance the excessive amount of time spent seated at work[7,8]. Standing desks have been suggested to increase slightly but significantly EE at work ($\approx$1.2 kcal.min^{-1})[9] compared with sitting position. However, this strategy may not benefit everyone to the same extent; inter-individual variability has been previously reported in energy during a sit-to-stand protocol[10,11]. Some individuals displayed a significant increase in EE during a steady-state standing position compared to a sitting position, while only a small increase in EE was detected in others in response to this postural change. These previous results from Miles-Chan and al.[10,11] raised questions regarding standing as an effective strategy to increase EE in the overall population. The variability in EE adaptation has been associated with some health parameters such as body fat mass that is positively correlated with the energy cost of standing posture in healthy

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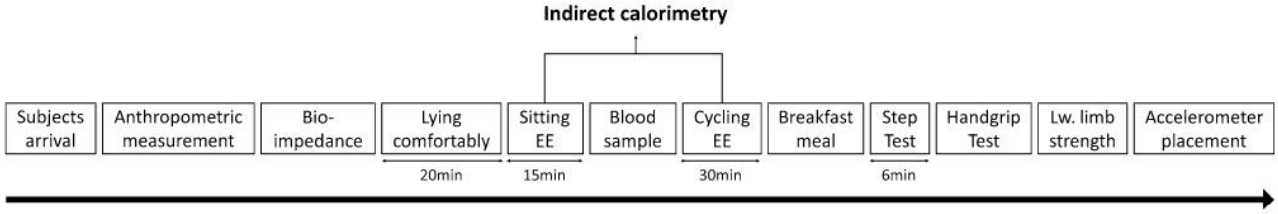

Figure 1. Schematic representation of the experimental design. EE, energy expenditure; Lw., lower.

inactive individuals[12]. Several studies have questioned the energetic cost of other different dynamic workstations such as walking on a treadmill or cycling desk[9,13]. While these studies obviously reported a substantial increase in EE (≈2–4 kcal.min^{-1}) compared to seating position[9,14,15], cycling desks have been suggested to be the best active workstation in terms of work and psychobiological performances[13]. Nevertheless, none of the studies investigating EE during cycle-desk utilization have identified the parameters that could explain these different energy profiles. Several authors have noticed that training status can influence cycling gross efficiency[16,17], with higher trained subjects being more efficient (i.e. more thrifty). However, the exercise intensities used in these studies are moderate to high and might not be representative of EE adaptations during low intensity exercise on a cycle-desk. Hence, it remains unknown whether the energetic profile of individuals during low intensity activities such as cycle-desk can be explained by specific anthropometric, body composition, cardiometabolic parameters or physical fitness. Indeed, understanding the characteristics of individuals' energetic profiles will enable a better optimization and individualization of active-desks strategies. In this context, the present study is the first to aim at comparing body composition, the cardiometabolic and physical fitness profile of individuals characterized as spenders *versus* non-spenders during a low intensity cycle-desk exercise, based on EE measurement. We hypothesized that participants with a more efficient energy profile will present healthier body composition, metabolic health and physical fitness.

Methods

Participants. Twenty-eight healthy women, administrative employees, with a body mass index (BMI) ranging from 18.5 to 29.9 kg/m^2 and aged between 18 to 60 years, participated in the present study. To be included in the study participants had to: i) be engaged in less than 150 min of moderate-to-vigorous physical activity per week based on self-reported data; ii) declare having regular menstrual cycles; iii) not be pregnant or lactating; iv) be free of any cardiovascular or metabolic disorders; v) not be dieting; vi) be free of any medication (excepted oral contraceptive); and vii) have a stable body weight (< 3 kg change during the 6 months prior to screening). This study was approved by the French ethical committee (Comité de Protection Personne Ile De France VIII 19 09 66) and all methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained for all participants in the present study.

Experimental design. After a full medical examination to assess eligibility, all subjects were asked to join the laboratory (laboratory AME2P, Aubière, France) for an experimental visit between January 6th and January 24th, 2020. Subjects were asked to keep their habitual daily activities, avoid any stressful situations and not consume caffeine for the 24 h prior to the test day. All participants completed this experimental session (Fig. 1) during the follicular phase of their menstrual cycle. Subjects reported to the laboratory at ~ 08.00 am, after a 12-h overnight fast. Evaluation started with body composition assessment and EE at rest was then investigated. Blood sample was obtained before a light intensity cycling exercise during which EE was measured. Participants' physical fitness was evaluated on the same day after a standardized breakfast meal. Finally, before leaving the laboratory, participants received an accelerometer to be worn for the following 7 days in order to assess their daily physically active and sedentary time.

Anthropometric measurement and body composition. Height was measured with a stadiometer at the nearest 0.1 cm, waist circumference (WC) was measured with a tape measure at the nearest 0.5 cm and WC to height ratio (WHtR) was calculated. Body weight was assessed using a calibrated scale (SECA, Les Mureaux, France) and fat mass percentage (%FM) and fat-free mass (FFM-kg) were evaluated by bioelectrical impedance (Tanita MC-780, USA, Arlington Heights), following the manufacturer's instructions.

Energy expenditure and substrate oxidation. After calibration of the device, indirect calorimetry with a facemask (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) was used to measure VO_2 and VCO_2 for EE and substrate oxidation assessment. A heart rate monitor (Polar A300, Polar, Kempele, Finland) was used for the length of the experiment. Prior to resting condition subjects were sitting quietly for 15 min. For resting condition, subjects were lying comfortably in a deckchair in a thermoneutral environment for at least 20 min. After this period, subjects were asked to stay calm, not speak and avoid any movement. Gas exchanges were recorded for 15 min minimum and only the last 5 min were analyzed as previously suggested[18] and were defined as "Rest" time measure.

During the exercise condition, subjects were submitted to a 30-min light exercise using a cycle-desk (DeskCycle, 3D Innovations LLC., Greeley, CO, USA) with a resistance set at 2 out of 8 per design of the ergometer and a revolution per minute (RPM) at 50 during the whole test, representing a power of ~ 16 Watts. An investigator supervised that participants respected the speed during the cycling test and reported at the end of the exercise the distance covered to ensure the test condition was similar between subjects. After the 30-min exercise testing, subjects had 1-min of recovery. Gas exchanges were measured during the entire exercise test and recovery period. EE, using Weir's equation[19], respiratory quotient (RQ; VCO_2/VO_2) and substrate utilization, using Péronnet & Massicotte equations[20] were calculated for the whole 30-min exercise session and also at rest, and after 5 (Start), 10, 20, 30 min of exercise. Mean values of the last 2 min of each period were considered for analysis as done in previous studies[21]. The first minute of recovery was also considered for analysis.

Cardiometabolic outcomes. Systolic and diastolic blood pressures were measured in a seated position using an auditory stethoscope with a blood pressure cuff adapted to the arm circumference. Subjects remained comfortably installed on a deckchair to collect a fasting blood sample. Plasma glucose, triglycerides, light-density lipoprotein cholesterol (LDL-cholesterol), high-density lipoprotein cholesterol (HDL-cholesterol) and total cholesterol were measured by enzymatic commercial assays. Insulin was assessed by chemiluminescent enzyme immunoassays. The enzymatic kits can be found in Supplemental file 1. All blood samples were centrifuged and plasma was kept frozen in aliquots at − 80 °C prior to analyses. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the following formula: fasting blood insulin (mU/L) x fasting blood glucose (mmol/L) / 22.5[22].

Physical fitness. *Aerobic fitness.* Participants performed a 6 min step test as described before[23]. Participants wore a heart rate monitor (Polar A300, Polar, Kempele, Finland) to continuously record heart rate from the start to the end of the test, 30 s and 1 min in recovery.

Upper and lower limb strength. Participants performed a handgrip test as described in previous studies[24]. Then, participants were seated with a hip joint at 105° of flexion and were attached on the trunk, the hip and the left leg to the dynamometer chair (Biodex System 2, Biodex, Shirley, USA) with Velcro straps. Torque was measured on isometric 3 s-Maximum Voluntary Contraction (MVC) and on concentric MVC at a velocity of 60°/sec and 120°/sec.

Daily physical activity and sedentary time. From the day after the experiment, every subject was asked to wear triaxial accelerometers (ActiGraph wGT3X-BT, ActiGraph, Inc., Pensacola, FL) during 7 days with at least one weekend day. Participants wore the device on the right hip[25] on an elastic belt. Data were collected at a frequency of 60 Hz and converted to counts per 1 s epoch using the manufacturer's software (ActiLife version 6.13.4). Non wear time was defined as 90 min of 0 count per minute (cpm) with an allowance of 2 min of activity when it is placed between two 30-min windows of 0 cpm[26]. To be accepted in the analysis, accelerometer data had to be at least 4 days (including 1 weekend day) of wear with a monitor wear time of $\geq$ 10 h/day (600 min/day)[27]. SB was calculated with the vertical axis and PA with vector magnitude. SB was defined as $<$ 150 counts min^{-1}[28], light intensity PA (LIPA) was obtained by subtracting SB and data below 2689 counts min^{-1}, MVPA was defined as 2,690–6166 counts min^{-1}, vigorous PA (VPA) was defined as $<$6467 counts min^{-1}[29].

Statistical analyzes. The sample size was estimated in order to compare the metabolic and physical profile of individuals characterized as high spenders (H-Spenders) versus low spenders (L-Spenders) based on EE during a cycle-desk low intensity exercise. To highlight significant differences greater than 1 point effect-size, 14 participants by group (H-Spenders vs. L-Spenders) were needed for 80% satisfactory statistical power and a two-sided type I error at 5%.

Statistical analysis was performed using Stata software (version 15, StataCorp, College Station, Texas, USA). Data were presented as mean and standard deviation. The Shapiro–Wilk test was used to test the assumption of distribution normality for quantitative parameters. Energy profile was determined by categorizing difference between EE at rest and 27 min of exercise (3-27 min) (Delta Exo-Rest) according to statistical distribution, i.e. to median of the sample[30,31]. This categorization enabled to have two different groups: High Spenders (H-Spenders) and Low Spenders (L-Spenders). The comparisons between groups (above versus below the median value), were performed by repeated-measures ANOVA and post-hoc Bonferroni test was used for multiple comparisons with significance levels set at $p < 0.05$. The statistical tests were two-sided, with type I error at 0.05. Then, a sensitivity analysis was conducted to guaranty that these analyzes realized according to median value were robust and that conclusions can be supported by the results. Delta Exo-Rest was categorized according to values ranged between interquartile ranges. The comparisons were performed as aforementioned. More precisely, for each value of Delta Exo-Rest between first and third quartile, continuous variables were compared among $<$ or $\geq$ of each value of Delta Exo-Rest. The results were expressed as Hedges' effect size (ES) and 95% confidence intervals, and were interpreted according to Cohen's rules of thumb, which defines effect-size bounds as: small (ES: 0.2), medium (ES: 0.5) and large (ES: 0.8: grossly perceptible and therefore large). Multivariate analysis was conducted using multiple linear regression to adjust results on weight of participants. The assumption of residuals normality was analyzed as aforementioned. When appropriate, a logarithmic transformation was applied. As these analyzes could be considered as exploratory, individual p-values have been reported without applying any mathematical correction but with specific attention to the magnitude of differences (i.e. ES), according to several works reported in the literature like those discussed by Bender and Lange[32]. Furthermore, principal component analysis was also performed to investigate relationships between quantitative variables using R software (R Foundation for Statistical Computing, Vienna, Austria). This statistical method was useful for analyzing assets as elements of

Variables	Low spenders	High spenders
N	14	14
Age (years)	41.9 (10.9)	37.7 (7.6)
Height (cm)	164.4 (4.7)	163.8 (7.3)
Body weight (kg)	58.4 (4.6)	64.5 (11.8)
BMI (kg/m^2)	21.6 (1.7)	23.9 (3.8)
Body fat mass (%)	25.9 (5.9)	31.5 (6.6)*
Body fat-free mass (kg)	40.9 (2.4)	41.4 (4.8)
Waist circumference (cm)	73.2 (6.0)	82.0 (11.3)
Waist circumference/height	0.44 (0.04)	0.50 (0.07)*
Systolic blood pressure (mmHg)	112.1 (5.8)	121.1 (14.9)
Diastolic blood pressure (mmHg)	70.0 (6.0)	76.1 (8.4)
Glucose (mmol/L)	4.79 (0.32)	5.12 (0.90)
Insulin (mIU/L)	4.04 (1.72)	9.25 (6.46)**
HOMA-IR	0.86 (0.36)	2.30 (2.35)**
Total cholesterol (g/L)	1.73 (0.45)	1.68 (0.25)
HDL-Cholesterol (g/L)	0.66 (0.09)	0.54 (0.13)*
LDL-Cholesterol (g/L)	0.99 (0.24)	1.00 (0.27)
Triglycerides (g/L)	0.83 (0.38)	0.72 (0.28)

Table 1. Characteristics of the study population. BMI, body mass index; HOMA-IR, homeostasic model assessment of insulin resistance; HDL, high-density lipoprotein cholesterol; LDL, light-density lipoprotein cholesterol. Values are presented as mean score (standard deviation) or percentage. Boldface indicates statistical significance (*$p < 0.05$, **$p < 0.01$), respectively with Mann–Whitney test.

quantitative variables in order to i) uncover the underlying relationships and structures of the measured variables (latent constructs) and ii) to aggregate subjects into clusters such that each cluster represents a topic.

Results

Anthropometric, body composition and cardiometabolic outcomes.

H-Spenders and L-Spenders were aged 37.7 ± 7.6 and 41.9 ± 10.9 y.o., respectively, with a mean BMI of 23.9 ± 3.8 and 21.6 ± 1.7 kg/m^2. H-Spenders had a higher percentage of body fat mass ($p = 0.034$) and WHtR ($p = 0.025$) and lower fasting plasma concentration of HDL-C ($p = 0.014$) compared to L-Spenders (Table 1). A lower insulin sensitivity was observed for H-Spenders compared to L-Spenders, as indicated by greater plasma insulin concentrations ($p = 0.002$) and HOMA-IR ($p = 0.002$) values (Table 1). No other between-group significant difference was reported in body composition and cardiometabolic outcomes (Table 1).

Daily physical activity, sedentary time and physical fitness.

As displayed in Table 2, no significant difference was observed between the two groups for aerobic fitness, upper and lower limb strength, total and segmented (by intensities) physical activity levels and sedentary time (Table 2). Based on the recorded physically active and sedentary time, our population can be considered sedentary and physically inactive[1].

Energy expenditure, heart rate and substrate oxidation.

Overall, Delta Exo-Rest for EE showed large variability (0.5 to 1.8 kcal.min) (Fig. 2). Mean EE during the 30-min exercise increased significantly compared to mean resting EE in both H-Spenders (2.26 ± 0.2 *vs* 0.98 ± 0.12 kcal/min, $p < 0.001$) and L-Spenders (1.91 ± 0.15 *vs* 0.93 ± 0.11 kcal/min, $p < 0.001$). There was no between-group difference in EE at rest (0.98 ± 0.12 *vs* 0.93 ± 0.12 kcal/min, respectively). However, H-Spenders had higher EE than L-Spenders at every time point of the exercise test: start (2.38 ± 0.19 *vs* 1.93 ± 0.16 kcal/min, $p < 0.001$, respectively), 10 min (2.26 ± 0.18 *vs* 1.92 ± 0.13 kcal/min, $p < 0.001$, respectively), 20 min (2.21 ± 0.22 *vs* 1.88 ± 0.15 kcal/min, $p < 0.001$, respectively), and 30 min (2.18 ± 0.17 *vs* 1.92 ± 0.15 kcal/min, $p < 0.001$, respectively) (Fig. 3A). At 1 min-recovery, EE was not significantly different between the groups (1.56 ± 0.30 *vs* 1.39 ± 0.20 kcal/min, H-Spenders *vs* L-Spenders, respectively).

The light cycling exercise significantly increased heart rate compared to resting position in both H-Spenders (86 ± 11 *vs* 70 ± 12 beats/min, $p < 0.001$) and L-Spenders (81 ± 10 *vs* 68 ± 9 beats/min, $p < 0.001$) with no differences between the two groups. This increase was consistent across the entire duration of cycling for both groups (Fig. 3B).

RQ was similar between H-Spenders and L-Spenders at rest (0.84 ± 0.05 *vs* 0.83 ± 0.04, respectively) but was significantly higher in H-Spenders during the whole duration of exercise compared to L-Spenders ($p = 0.021$) (Fig. 4A). Taking all data together, there was a time effect ($p = 0.009$) for carbohydrates (CHO) oxidation, which was significantly higher during exercise compared to rest ($p = 0.008$) and recovery ($p = 0.006$). Resting CHO oxidation was significantly higher in H-Spenders compared to L-Spenders (3.33 ± 1.2 *vs* 2.82 ± 0.94 mg/min/kgFFM, $p = 0.017$, respectively). No significant difference was observed between groups at start, while H-Spenders oxidized significantly more CHO than L-Spenders during cycling at 10 min (6.52 ± 2.28 *vs* 4.53 ± 1.48 mg/min/

Variables	Low spenders	High spenders
N	14	14
Valid days of accelerometer wear	5.7 (0.4)	6.0 (0)
Weekdays	3.9 (0.3)	4.0 (0)
Weekend days	1.8 (0.4)	2.0 (0)
Number of minutes of accelerometer data (min/day)	352.9 (64.3)	368.9 (55.4)
Sedentary time (%/daily waking hours)	87.8 (2.9)	87.9 (3.1)
Total physical activity (%/daily waking hours)	12.2 (2.9)	12.0 (3.1)
LPA (%)	3.1 (1.1)	3.4 (1.1)
MVPA (%)	7.9 (1.9)	7.7 (2.7)
VPA (%)	1.2 (0.5)	0.9 (0.4)
Handgrip dominant hand (kg)	29.1 (4.7)	29.3 (4.7)
Handgrip non-dominant hand (kg)	28.0 (4.8)	26.5 (5.0)
Rest heart rate step test (bpm)	65.8 (6.8)	74.8 (12.7)
Heart rate step test (bpm)	147.9 (18.0)	160.3 (16.7)
Heart rate step test + 30 (bpm)	124.5 (19.9)	136.0 (19.3)
Heart rate step test + 60 (bpm)	106.2 (20.1)	118.1 (17.6)
Isometric strength (nm)	136.1 (31.7)	131.1 (36.6)
Isokinetic power 60°/sec (w)	142.7 (33.2)	140.1 (34.0)
Isokinetic power 120°/sec (w)	236.5 (55.7)	215.1 (60.5)

Table 2. Physical activity level, sedentary time and physical fitness of the study population. LPA, light intensity physical activity; MVPA, moderate-to-vigorous physical activity; VPA, vigorous physical activity. Values are presented as mean score (standard deviation) or percentage.

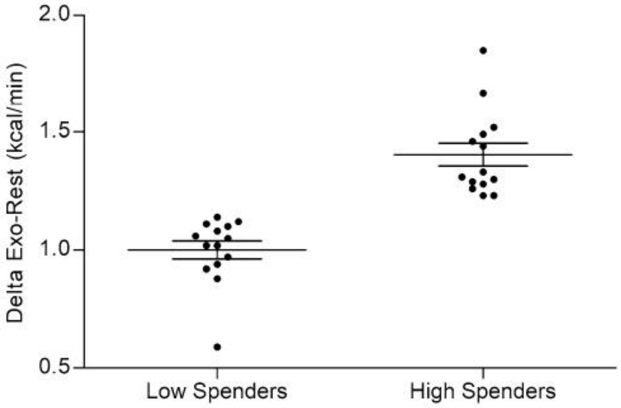

Figure 2. Characterization of Delta Exo-Rest between H-Spenders and L-Spenders. Data are presented as mean ± SEM.

FFM, p = 0.009, respectively), 20 min (6.52 ± 2.34 *vs* 4.79 ± 1.47 mg/min/kgFFM, p = 0.049, respectively) and 30 min (6.47 ± 2.15 *vs* 4.14 ± 1.38 mg/min/kgFFM, p = 0.008, respectively). No significant difference was reported at recovery between groups and compared to rest.

There was also a time effect for lipid oxidation, which was higher during exercise compared to rest for both H-Spenders (3.88 ± 1.55 *vs* 1.28 ± 0.33 mg/min/kgFFM, p < 0.001) and L-Spenders (3.85 ± 1.48 *vs* 1.27 ± 0.34 mg/min/kgFFM, p < 0.001). A group effect was noticed at the start of exercise and during recovery, with H-Spenders oxidizing more lipid than L-Spenders at start (5.94 ± 1.69 *vs* 4.76 ± 1.03 mg/min/kgFFM, p = 0.030, respectively) and oxidizing less lipid than L-Spenders during recovery (2.1 ± 0.44 *vs* 4.84 ± 2.34 mg/min/kgFFM, p = 0.002, respectively). No significant difference was reported for any other time of the exercise test.

Relative to total EE at rest, there was no significant difference in CHO oxidation in percentage between H-Spenders and L-Spenders (53.5 ± 17.8% *vs* 49.5 ± 14.9%, p = 0.26) or for lipid oxidation (46.5 ± 15.5% *vs* 50.4 ± 12.4%, p = 0.46) (Fig. 4B). During exercise, CHO oxidation was representing a greater percentage of total EE (44 ± 10.9% vs 35.7 ± 8.6%, p = 0.050) and lipid oxidation a lower percentage (56 ± 8.9% vs 64.3 ± 7.2%, p = 0.045) in H-Spenders compared to L-Spenders (Fig. 4C). No specific correlation were found between EE or substrate oxidation parameters and body composition, anthropometric data or blood parameters.

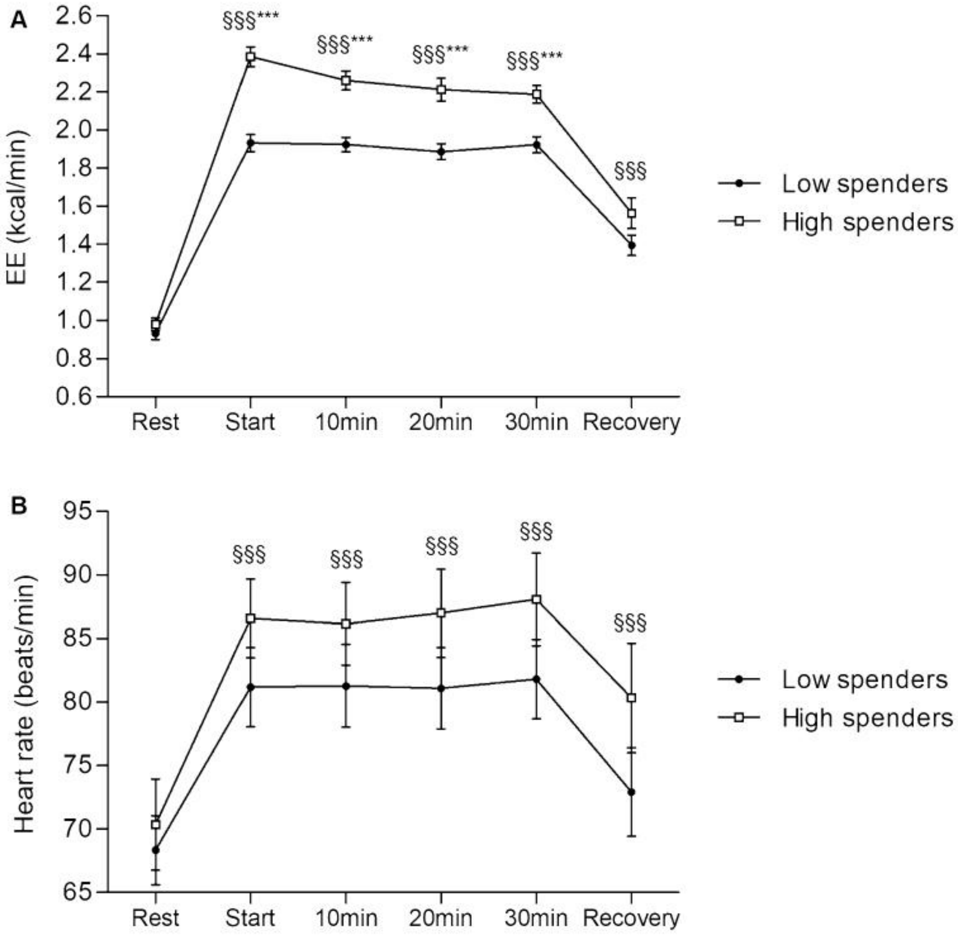

Figure 3. Comparison of EE (**A**), heart rate (**B**), from resting condition to light cycling exercise and recovery in each EE response group: H-Spenders and L-Spenders. Data are presented as mean ± SEM. §§§, time effect at $p < 0.001$; ***, significantly different between low spenders and high spenders at $p < 0.001$.

Principal component analysis. Lastly, the associations between the different parameters studied were illustrated by a principal component analysis (Fig. 5). Our data has shown a strong correlation between Delta Exo-Rest and some cardiometabolic parameters, such as inulin, HOMA-IR, LDL-cholesterol, glucose and triglycerides (Fig. 5). Also, the variability of energy expenditure between rest and low intensity cycling was strongly associated with higher values of body composition and anthropometric parameters (fat mass, fat-free mass, BMI, WC and WC/height) (Fig. 5).

Discussion

Active workstations are currently promoted to decrease office-related sedentary time and increase PA in a public health perspective. The aim of the present study was to examine associations between energy expenditure during a low intensity exercise on a cycle-desk device and body composition, cardiometabolic parameters and physical fitness of tertiary employees. Our data shows that two energetic profiles (H-Spenders or L-Spenders) can be identified in premenopausal women. More importantly, those two profiles show significant differences in anthropometric data, body composition (fat mass and WHtR) and metabolic outcomes (insulin, HOMA-IR, and HDL-Cholesterol), with H-Spenders presenting a less healthy metabolic profile.

Our results show that a light intensity cycle-desk exercise can significantly increase EE between 1.9 and 2.4 METs compared to resting. This result is in line with previous studies[14,33] and demonstrates that light intensity cycling allows to increase EE above EE associated with sedentary activities (i.e. 1.5 METs). A number of studies have questioned the effect of cycle-desk use on EE[14,21,34] but, none of them has looked for the potential factors that could explain this EE variability. Heterogeneity in energy responses has been reported in other studies from a sitting position to a steady-state standing position[10,11] with individuals characterized as "energy-savers" or "energy-spenders". While studies of Miles-Chan et al.[10] reported only 18% of their subject having a significant increase in EE compared to sitting (increase > 5% resting EE), all subjects of our study significantly increased their EE during the low-intensity cycling session. Differences in the magnitude of responses between the two studies are likely explained by the higher energetic demand induced by cycle-desk used in the present study compared to the standing position alone (1.9 to 2.3 METs vs ~ 1.2 METs)[9].

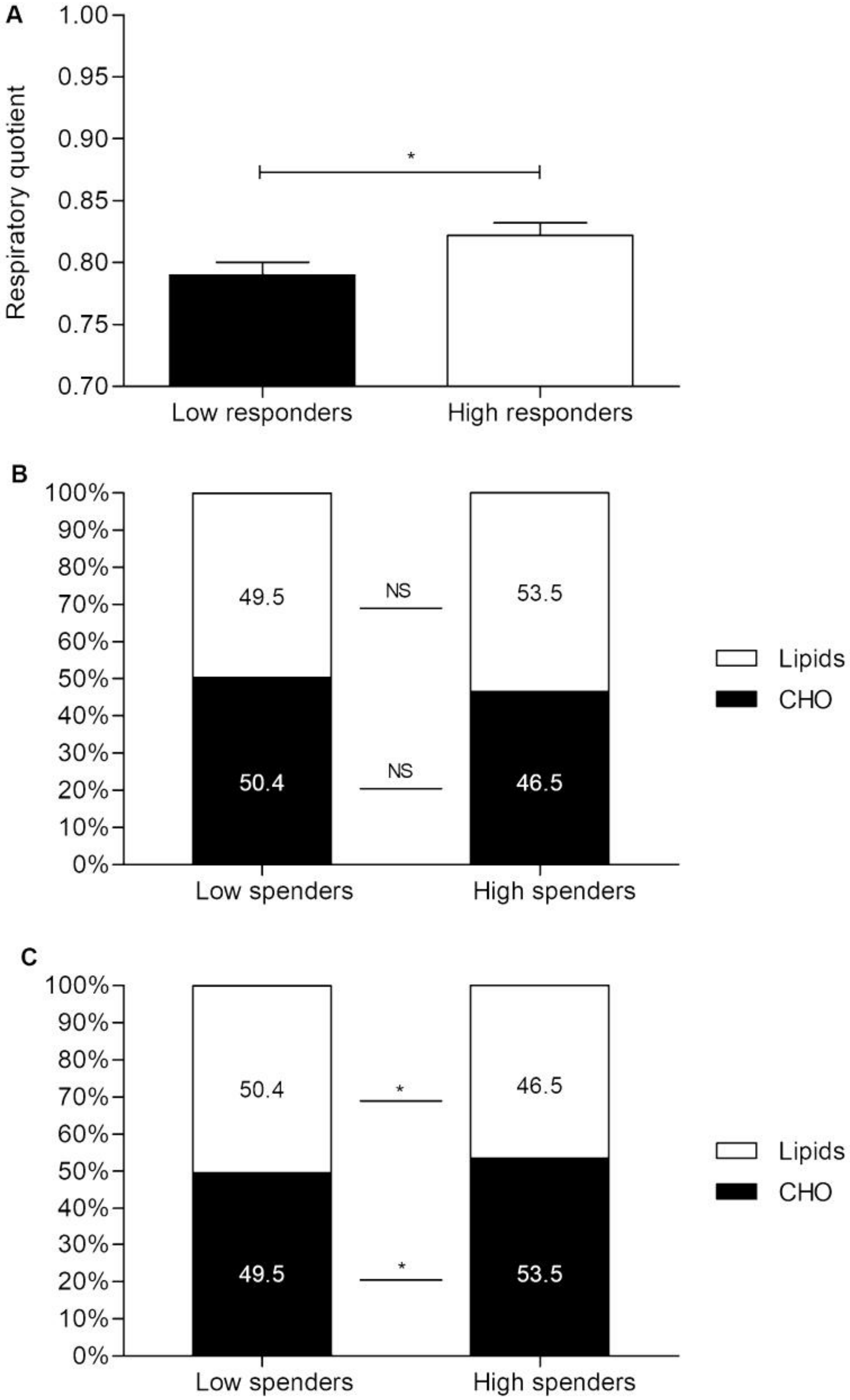

Figure 4. Respiratory quotient (**A**) during light cycling exercise. Substrate oxidation during Rest (**B**) and light cycling exercise (**C**). (**A**) data are presented as mean ± SEM. (**B**) and (**C**) data are expressed as mean percentage of CHO and lipids consumption relating to total energy expenditure. NS, not statistically significant; *, significantly different between low spenders and high spenders at $p < 0.05$.

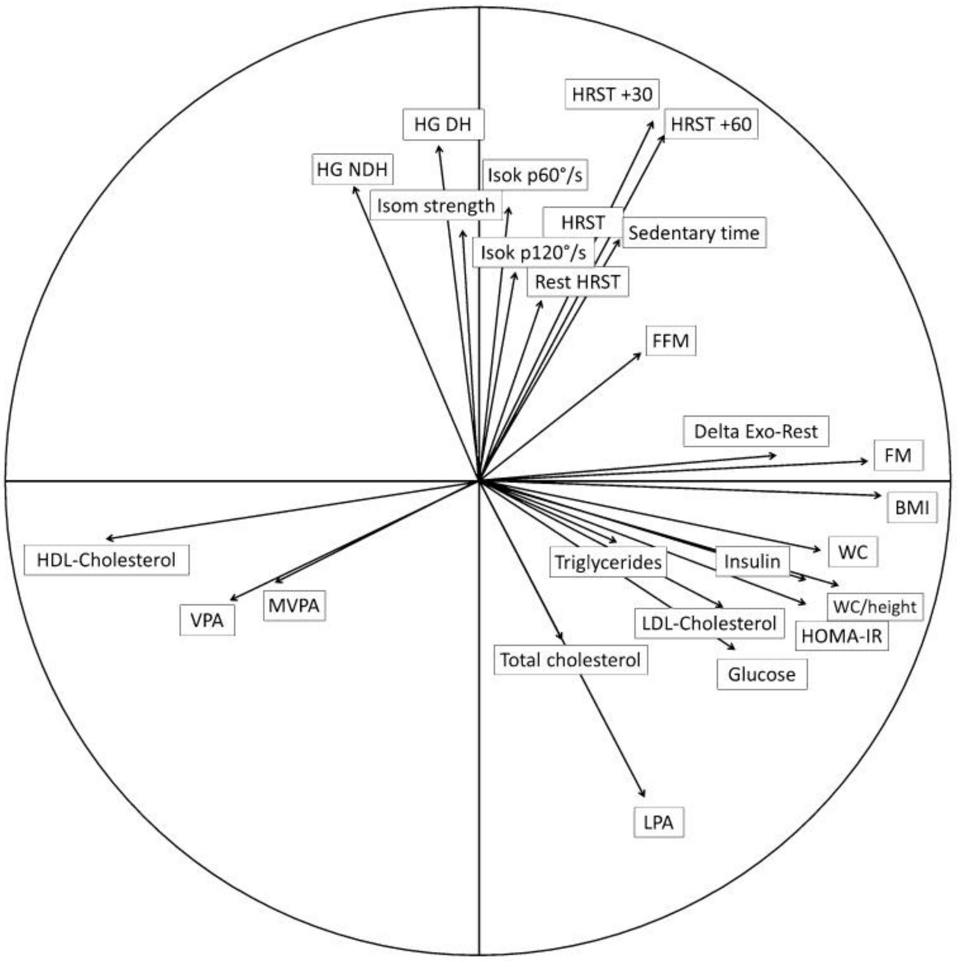

Figure 5. Principal component analysis of the study parameters. BMI, body mass index; DH, dominant hand; FFM, fat-free mass; FM, fat mass; HG, handgrip; HOMA-IR, homeostasic model assessment of insulin resistance; HDL, high-density lipoprotein cholesterol; HRST, heart rate step test; Isok, isokinetic; Isom, isometric; LDL, light-density lipoprotein cholesterol; LPA, light intensity physical activity; MVPA, moderate-to-vigorous physical activity; NDH, non-dominant hand; VPA, vigorous physical activity; WC, waist circumference.

Light-intensity cycling was more demanding for H-Spenders who were eliciting higher EE at each period of exercise than L-Spenders. During exercise, H-Spenders oxidized more CHO, both in total amounts and relatively to EE, but a lower percentage of lipids compared to the L-Spenders, while H-Spenders had significantly more fat mass than L-Spenders. Relationships between fat mass percentage, body weight and substrate oxidation during exercise have been investigated in several studies with no clear association between these parameters[35,36]. Studies comparing substrate oxidation during exercise in women with normal weight and overweight did not show clear differences[35,36]. It suggests that excess of fat mass does not necessarily result in a decrease in the ability to oxidize lipids. However, fat mass localization in normal or overweighed subjects seems to be more associated with substrate oxidation during exercise[37,38] than percentage of fat mass per se, with lower body fat mass profile being associated with better ability to oxidize lipids. In this line, we found that H-Spenders displayed higher %FM and WHtR, suggesting higher abdominal repartition of fat mass in individuals with this energy profile. The ability to rely predominantly on lipids or carbohydrates during submaximal exercise has been associated with the concept of metabolic flexibility, which is defined as the capacity to adjust fuel utilization to changes in fuel availability[39]. Metabolic state associated with glucose intolerance or insulin resistance has been shown to favor CHO oxidation during low intensity exercise compared to control subjects[40] and has been associated with metabolic inflexibility[41]. The metabolic challenge induced in our study by a 30-min low intensity cycling exercise suggests that H-Spenders are less metabolically flexible than L-Spenders as they are less able to rely on lipids during a low intensity exercise[42]. Physical fitness and training status are also known to influence the ability to preferentially rely on lipids during low and moderate intensity exercise[43]. Thus, the H-Spenders and L-Spenders profiles could have been explained by differences in physical capacities of the subjects. This appears however unlikely here since heart rate during step test and higher and lower limb strength did not differ significantly between the two groups.

The potential mechanisms explaining heterogeneity in energy profile have been poorly investigated in previous studies questioning strategies to decrease SB during work time. Miles-Chan et al.[10] did not find any association between body weight or height and EE when comparing energy cost in sitting *vs* standing positions. In a second study of the same research group, the energy cost of standing posture maintenance was positively correlated with body weight and WC[12]. Recently, Amaro-Gahete et al.[44] showed that FFM could partly explain differences in EE profiles in sitting *vs.* standing position. Although H-Spenders had a higher percentage of fat mass, no difference in FFM was observed. These results are also concordant with the study of Chen et al.[45], in which were reported relationships between energy efficiency and fat mass during walking, with subjects with obesity having decreased work efficiency compared to individuals with normal-weight during normal-speed walking. We further examined the cardiometabolic parameters of the two energy profiles. Our results suggest that H-Spenders showed a less healthy cardiometabolic profile as indicated by higher levels of fasting insulin, HOMA-IR and lower level of HDL-Cholesterol than L-Spenders. Metabolic profile and substrate oxidation during exercise of H-Spenders further feature similarities with those of subjects with obesity and/or type 2 diabetes[40].

Individualization of exercise programs is a cornerstone of health management. Our results suggest that physical activity level and fitness capacities are not sufficient to discriminate people and that an energy evaluation at rest and during exercise should be assessed to personalize prescription. In light of our results, we can assume the H-Spenders benefit more from the same cycle-desk program than L-Spenders. Depending on the energy profile, it could be expected that cycle-desk use recommendations may need to differ in terms of time and/or intensity of pedaling. Given the increased demand and/or necessity in the utilization of active desks, this could have important implications for metabolic health management.

One potential limitation needs to be considered. We only studied women, thus those results are only applicable to the female population. However, Miles-Chan et al.[10] reported different energetic profiles among male individuals during an activity at a lower intensity suggesting that the existence of different energy profiles might not be sex dependent. Nevertheless, the relation with body composition or metabolic profile could depend on this factor as shown by Chen et al.[45]. It is well known that hormonal status affects EE and two of our participants were taking oral contraceptives. Currently, there is no clear scientific evidence that oral contraceptives could induce modification of EE at rest or during exercise.

Conclusion

This study confirms that light cycling exercise enables to increase EE compared to resting but, inter-individual heterogeneity exists in the magnitude of energetic response. Differences in physical fitness, habitual time spent active or sedentary are not explaining this inter-individual variability. However, female individuals who spend less energy during a low intensity cycling activity present a healthier metabolic profile than those who displayed higher EE. Identification of energy profile could represent a strategy to better individualize the use of dynamic workstations to optimize EE during workdays. Future studies will need to investigate whether long-term utilization of light-intensity cycling desk at work can improve metabolic health outcomes of sedentary office workers, especially those with less healthy metabolic profiles.

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Author contributions

T.G., L.M., M.D. and D.T. designed the study; T.G., P.B., E.L.R. and A.B. performed the experiments; T.G., L.M., D.T., L.I., B.P., A.B. and M.D. contributed significantly to the writing and revision of the manuscript. All the authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Annexe 3: The role of physical activity in the regulation of body weight: The overlooked contribution of light physical activity and sedentary behaviors

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REVIEW

OBESITY Reviews WILEY

The role of physical activity in the regulation of body weight: The overlooked contribution of light physical activity and sedentary behaviors

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Summary

The role of physical activity (PA) in the regulation of body weight is still a major topic of debate. This may be because studies have essentially focused on the effects of moderate/vigorous PA (MVPA) on body weight while overlooking the other components of PA, namely, light-intensity PA (LPA, daily life activities) and sedentary behaviors (SB, too much sitting). In this review, we will (i) describe the history of changes in PA behaviors that occurred with modernization; (ii) review data from cross-sectional and longitudinal studies that examined the associations between PA, SB, and measures of obesity; (iii) review interventional studies that investigated the effects of changes in PA and SB on body weight and adiposity; and (iv) discuss experimental studies that addressed potential biological mechanisms underlying the effects of PA and SB on weight regulation. Overall recent findings support the importance of considering all components of PA to better understand the regulation of energy balance and suggest an important role for LPA and SB in addition to MVPA on body weight regulation. Longitudinal large-scale rigorous studies are needed to advance our knowledge of the role of PA/SB in combating the obesity epidemic.

KEYWORDS
energy balance, physical inactivity, sedentary behaviors, weight management

1 | INTRODUCTION

Although obesity is a complex multifactorial disease, weight gain can only result from chronic positive energy balance, that is, calorie consumption greater than energy needs. The causes of this imbalance however remain unclear. Over the past few years, a debate has been growing in the scientific community and the media on the relative contribution of increased energy intake (EI) versus reduced energy expenditure (EE) to the obesity epidemic. Although the importance of physical activity (PA) in weight management is generally accepted, the role of PA in weight gain is more controversial.[1–7] Some investigators promote a diet-centric view according to which the global obesity epidemic observed over the past decades is due to increases in EI rather than to declines in EE due to a fall in habitual levels of PA. Alternatively, Rowland proposed the "activity-stat" concept in 1998,[8] in which total daily EE (TDEE) is homeostatically regulated, that is, controlled around a fixed value. Pontzer et al.[9] recently proposed that TDEE is rather constrained. According to this theory, although EE increases with PA at low activity levels, it plateaus at higher activity levels as the body adapts to maintain TDEE within a narrow range. High activity levels may be offset by decreases in the other

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Abbreviations: BM, body mass; EE, energy expenditure; EI, energy intake; LPA, light physical activity; MET, metabolic equivalent; MVPA, moderate-to-vigorous physical activity; NWCR, National Weight Control Registry; PA, physical activity; PAL, physical activity level; SB, sedentary behaviors; TDEE, total daily energy expenditure; WHO, World Health Organization.

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components of TDEE including resting metabolic rate (the minimal amount of energy required to ensure vital functions) and diet-induced thermogenesis (the energy required to assimilate and store energy after a meal). This model has been used to explain why increased levels of PA often have little impact on weight-loss strategies (about 1-2 kg).[10] Although the role of PA in the treatment of obesity is controversial, its benefits for preventing unhealthy weight gain and body weight regain following weight loss is more generally accepted.[11]

Our research group subscribes to the view that the constrained TDEE model is not necessarily incompatible with a key role of PA in body weight and composition management. The plateau has been observed at PA levels (PAL, defined as the ratio between TDEE and resting metabolic rate) of about 2.5–3.0, which are levels observed in professional athletes and competitors,[12] not in the general population whose PAL values are between 1.4–1.8.[13,14] Maintaining PAL values around 1.7–1.8 has been estimated to be enough to prevent body weight gain and regain after weight loss.[14–16] These observations support a role for PA in body weight regulation in the range of PALs observed in the general population. In addition, research has tended to overlook the contribution of nonexercise activities (mainly composed of light intensity physical activities [LPA], that is, PA associated with metabolic equivalents [METs] comprised between 1.6 and 2.9[17]), which correspond to activities of everyday life and any body movement, such as walking, taking the stairs, gardening,[18,19] or activities other than volitional structured exercise.[20,21] These nonexercise activities are known to account for a large component of EE even in sedentary individuals. In addition, time spent in LPA is negatively, but tightly, associated with time spent in sedentary behaviors (SB).[22] As trivial as it sounds, the more a person moves, the less time he/she spends in sedentary activities.

Research on SB has gained increasing attention over the past 10 years, especially with the development of activity monitors that allow to specifically measure this behavior. Although the terms physical inactivity and SB are used interchangeably,[23,24] they are fundamentally different. Physical inactivity is defined as engaging in less PA than necessary to meet current public health guidelines, that is, 150–300 min of moderate to vigorous or 75–150 min of vigorous PA or an equivalent combination of moderate-to-vigorous PA (MVPA, PA characterized by an EE > 3 METs).[17,25] By contrast, SB are defined as "any waking behavior characterized by an EE≤1.5 METs, while in a sitting, reclining or lying posture" based on the terminology consensus of the Sedentary Behaviors Research Network (SBRN).[26] Based on these definitions, an individual can paradoxically be both physically active and sedentary (Figure 1). Despite the wide promotion of PA recommendations, most people engage in high amounts of sedentary activities, that is, more than 55% of awake time.[27] In a meta-analysis regrouping 1 million men and women, Ekelund et al.[28] estimated that high levels of PA seem to be necessary to eliminate the increased risk of death induced by more than 8 h/day spent in SB, a duration commonly observed in office workers.[29] Despite the associations between

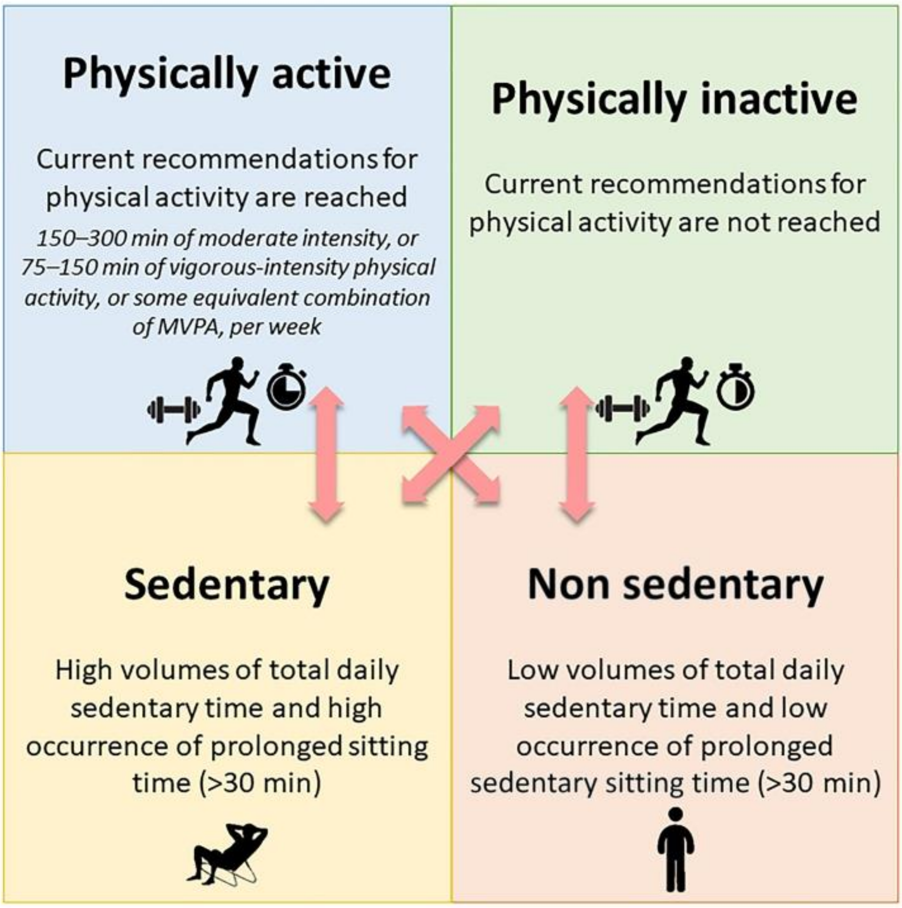

FIGURE 1 Schematic representation of the four observable behaviors across the spectrum of physical activity and sedentary behavior. Of note, no specific recommendations currently exist for being or not being sedentary. MVPA, moderate-to-vigorous physical activity

SB and chronic diseases,[30] there is a surprising lack of information on the roles that SB and physical inactivity play in the increasing prevalence of obesity.

The objective of this review is to summarize available data to discuss the role of PA in the obesity epidemic in adults, with a specific focus on SB and nonexercise LPA. We specifically (i) describe the changes in PA behaviors that have occurred over the past millennia; (ii) review data from cross-sectional and longitudinal studies that examined the associations between PA, SB, and measures of obesity; (iii) review the interventional studies that investigated the effects of changes in PA and SB on obesity markers; and (iv) discuss the experimental studies that addressed some of the potential biological mechanisms underlying the effects of PA and SB on weight regulation. Although this is not a systematic review, we did our best to provide an unbiased and balanced perspective by presenting key findings currently available to inform the debate on the role of PA/SB in body weight regulation.

2 | HISTORICAL CHANGES IN HABITUAL PHYSICAL ACTIVITY PATTERNS

2.1 | Physical activity patterns from ancient times to the present

Current human physiology and behavior are the results of natural selection in *Homo Sapiens* who emerged about 200,000 years ago. In the Paleolithic era (approximately 40–50,000 years ago), our ancestors hunted and gathered food. These activities required sustained activities at high levels of EE for 1–2 h/day. Moreover, inactive periods were probably composed of squatting, kneeling, or otherwise sitting in postures that required continuous very low to low-intensity muscle activity limiting the deleterious effects of sedentariness that are observed in current industrialized populations.[31] With the development of agriculture (approximately 10,000 years ago), humans needed to perform moderate-intensity activities for 6–8 h/day.[32] The former "intermittently active" lifestyle corresponding to cycles of short bouts of intense activities alternating with long resting periods was replaced by continuous and sustained bouts of moderate-intensity activity that were necessary to perform agricultural tasks without the benefit of modern technology. Lightfoot[32] estimated that nontechnological agricultural activity required 3–5 fold more active time than hunting/gathering. Although activity-related EE was similar between both preindustrial populations, it was significantly higher than what has been measured in modern westernized populations.[32]

Although PA patterns progressively changed over several millennia, rapid and major changes have occurred over the past 200 years. Since the Industrial Revolution (end of the 19th century in the United Kingdom), and more recently with the Great Acceleration (second half of the 20th century), industrial, technological, and digital advances have resulted in societal and behavioral changes in PA habits.[33] The former "traditional" environment, characterized by relatively scarce food and high EE, gave way to the modern "social" and "built" environment that promotes obesogenic behaviors. Today, being physically inactive does not jeopardize access to food due to the abundance of low-cost, high-fat, energy-dense food.[32] These changes in habitual PA patterns are however not uniform worldwide.[34] The prevalence of physical inactivity is negatively associated with the Human Development Index (HDI, a statistic composite index of life expectancy, education, and per capita income, used to rank countries into four tiers of human development).[35,36] Populations living in countries associated with the lowest HDI quartile have a significantly lower prevalence of physical inactivity than those in the highest quartile. Populations that have completed the epidemiological transition (i.e., a shift in the causes of death from deaths due to high child mortality and infectious diseases to deaths due to lifestyle-related and chronic diseases) along with their nutritional and physical activity transitions are particularly vulnerable to physically inactive and sedentary lifestyles.[37]

2.2 | Modern life: widespread adoption of sedentary and physically inactive lifestyles

In westernized populations, industrial and technological revolutions have engineered PA out of virtually every facet of daily life, that is, occupational (desk-bound jobs), domestic (dishwashers and washing machines), transport (cars), and leisure activities (video games, the internet, television.).[38] Based on body temperature measurement, Yegian et al.[39] estimated that MVPA decreased by 27 min/day since 1820 in the United States. By contrast, the global prevalence of physically inactive people has risen from 20% to 27.5% between 2011 and 2016 and keeps increasing.[40] These data based on self-reported population-based surveys likely overestimate PA.[41] For example, although 51% of the US population self-reported reaching recommended levels of PA in the National Health and Nutrition Examination Survey (NHANES study, 2003–2004), only 5% of individuals actually achieved these levels when data were objectively collected with an accelerometer.[42]

Along with this reduction in PA, time spent in sedentary activities has increased in every sphere of daily life. For example, time spent watching TV has increased by 61.4% in US adults between 1950 and 2000 reaching up to 8 h/day.[43] By contrast, the time children and adolescents spend watching TV decreased by approximately 23% between 1981 and 1997. This was associated with a concomitant decrease in free time by 12% mostly explained by an increased time away from home, primarily in school, day care, and after-school programs.[44] Nowadays, 86% of workers have sedentary jobs, spending 66% of their total work time sitting,[45] with a reciprocal reduction in physically active tasks. The expansion of the service sector of the economy has reduced time spent physically active in the workplace by 32% since 1960. A further drop of 45% is expected by 2030 in the United States and a reduction from 19% to 35% in the United Kingdom.[46] Although physical inactivity (i.e., not reaching current public health guidelines) has not further increased in US adults between 2001 and 2016,[40] self-reported daily time spent in SB (i.e., too much sitting) increased from 5.7 h in 2007–2008 to 6.4 h in 2015–2016.[47] Accelerometry-derived data reported more than 8 daily hours spent in SB with an average of 8.2 daily hours in the United States[48] and 8.8 h in Europe.[49] Thus, these changes in PA/SB have the potential to impact TDEE and increase the risks of the ill effects of SB.

2.3 | Consequences of the reduction of habitual physical activity on total daily energy expenditure

Several studies have tried to assess changes in TDEE over time. The measured EE of modern societies was compared to either the estimated EE of our ancestors or to the measured EE of modern populations who have maintained a pre-industrial lifestyle. Cordain et al.[50] estimated that the TDEE of modern humans is about 65% of the TDEE of people living in the late Paleolithic Stone Age. Based on this estimate, they wrote that our modern PAL is "below the level of physical exertion for which our genetically-determined physiology and biochemistry have been programmed through evolution". The same research group further showed that modern hunter-gatherers had higher levels of PA than individuals living in the modern United States. They estimated that the difference was equivalent to walking 19 km/day for an adult of 70 kg or 1,190 kcal/day.[50] Leonard[51] estimated that PAL was significantly lower in industrial as compared to modern subsistence populations, reflecting a less active way of life. He calculated that individuals living a subsistence lifestyle expended 411 kcal/day more than those living a modern lifestyle. By comparison, the American College of Sports Medicine (ACSM) PA recommendations accounts for only 69 kcal/day and 1 daily hour of intense exercise accounts for 330 kcal/day.[52] Egger et al.[53] compared EE in a group of actors paid to live like early Australian settlers to that of a group of modern sedentary office workers. He estimated that activity levels were on average 1.6-fold lower in industrialized populations than that of the forefathers from 150 years earlier. This was equivalent to a difference of 8 km/day of walking or about 380 kcal/day for a 70 kg male.

Between 1950 and 2000, occupations associated with low-intensity PA increased by more than 80% while those requiring high-intensity PA declined by 25%.[43] It has been estimated that these changes resulted in a decrease in work-related EE of 130 kcal/day over 50 years.[54] Some studies suggest this drop in occupational PA was offset by an increase in PA during leisure time.[43] However, other studies found that leisure PA only increased by 0.5% per year in Australian males between 1989 and 2011.[55] It was also estimated that leisure-time PA slightly increased in US adults between the 1990s and the 2000s associated with a substantial decline in household-, work-, and transport-related activities.[43] Although informative, all these data have to be taken with caution given they were self-reported. It is only in the 2000s that the objective measurement of daily PA patterns has become common with the development and growing availability of reliable activity montiors.[56]

Taken together, these studies suggest that there has been a major drop in PA over the millennia with a hypothetical average EE about 400–1,100 kcal/day greater in early *Homo Sapiens* compared to the modern "*Homo Sedentarius*" who suffers from "diseases of civilization"[32] (Figure 2). Decreases in PA and PA-related EE in high-income societies have been reported in more recent years, from the 1950s to the 1970s. On the other hand, data from NHANES showed an increase in EI of 168 and 335 kcal/day for men and women, respectively, between 1970 and 2000. These changes in PA and EI happened at a time when the prevalence of obesity increased in the early 1980s in the United States and Western Europe.[58] Of note, the chronic energy imbalance or energy gap (i.e., the difference between EI and EE) thought to be at the origin of the obesity epidemic in the United States is only about 50–100 kcal/day.[59] Although a parallel can

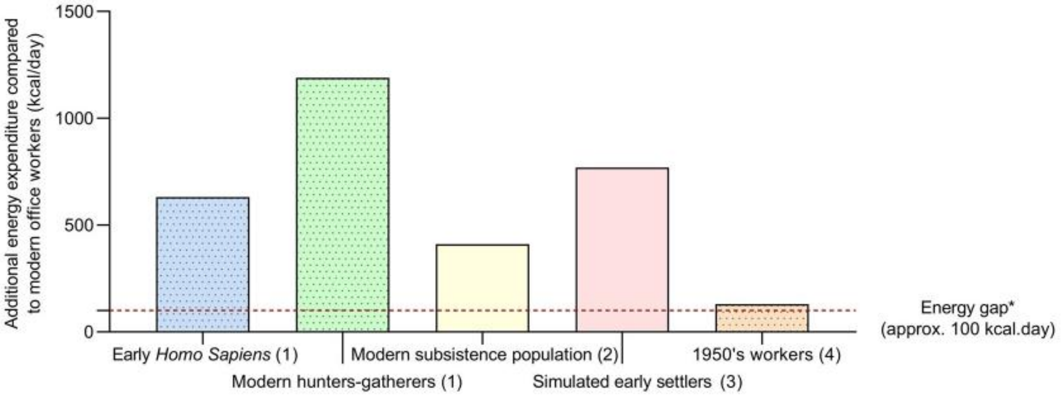

FIGURE 2 Schematic representation of the extra energy expended by early *Homo Sapiens*, modern hunter-gatherers, modern subsistence populations, and workers of the 1950s compared to the total daily energy expenditure of modern office workers. Spotted barres represent estimated data, and plain barres represent measured data. (1) Estimated by Cordain et al.[50]; (2) measured by Leonard[51]; (3) measured by Egger et al.[53]; (4) estimated by Church et al.[54]; * Hill (2013) estimated an energy gap (Energy intake − Energy expenditure) of about 100 kcal/day that likely explains the obesity epidemic at the population level.

be made between the transition in PA and the global rise in overweight and obesity prevalence, some objective data do not necessarily support a decline in TDEE over the past decades. When combining data using gold standard doubly labeled water (DLW)-derived TDEE collected between the 1980s and early 2000s, Westerterp and Speakman did not find any change in total or activity-related EE.[60] These observations and others have fed the debate on the role of PA in weight gain and its role in the obesity epidemic. However, it is possible that changes in PA and TDEE or activity-related EE occurred before the 1980s. The impact of the changes in PA over time on TDEE therefore remains an open question. Relationships between PA, SB, and epidemiological measures of obesity can however bring valuable insight into the influence of low levels of PA on body weight regulation (Box 1).

Box 1. **The physical activity transition**

- Drastic and rapid changes in physical activity and sedentary behavior occurred in every domain of daily life (work, leisure, daily life, etc.) over the past century.
- Only 20% of the global population currently reaches physical activity guidelines when objectively assessed.
- In high-income countries, people spend more than 8 h/day in SB.
- Likely, due to these changes in physical activity and sedentary behavior, the total daily energy expenditure of modern humans living in high-income countries is estimated to be lower than that of our ancestors, the early *Homo Sapiens*.
- The physical activity transition has created a mismatch between our evolutionary human history and the modern built and social environments, which contributes to the emergence of the "diseases of civilization."
- The role of the physical activity transition in the epidemic obesity is however still a topic of debate.

3 | ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY, SEDENTARINESS, AND MEASURES OF OBESITY PREVALENCE

3.1 | Associations from cross-sectional population studies

Most, but not all cross-sectional studies have reported negative associations between PAL and measures of obesity including body weight, body mass index (BMI), waist circumference, and adiposity in adults but also in adolescents and children.[61–65] For example, data on almost 3,000 children and adolescents assessed in the NHANES study showed that the least active group had the highest trunk fat mass.[66] Drenowatz et al.[67] observed in 430 adults (average age of 27.7 years) that the proportion of energy expended in MVPA is lower in people with overweight than in those with normal weight. On a larger scale, Füzéki et al.[68] reviewed the health benefits of LPA from the NHANES accelerometer dataset and included a total of 37 studies conducted in adults (16 studies in a general adult population, 14 in adults with chronic diseases, nine in older adults and one in pregnant women). Eight studies showed negative associations between time spent in LPA and waist circumference and four also reported negative associations with BMI. A fifth study observed a negative association between LPA and waist circumference but not with BMI. The authors concluded that inactive people should engage in PA of any intensity, the duration of the bouts being more important than intensity to protect against weight gain.[68] A recent review from Jakicic et al.[69] summarizing results from cross-sectional studies conducted in adults with overweight and obesity concluded that BMI was inversely associated with a total volume of MVPA when MVPA was accumulated in bouts lasting more than 10 min. These data, although suggestive of a relationship between PA and obesity, do not allow definitive conclusions to be drawn.

Only a few studies have examined the associations between time spent in SB and body weight. Anjana et al.[70] reported a negative relationship between self-reported sitting time and BMI and waist circumference in 543 Indian adults. Martínez-González et al.[71] conducted a survey of 15,239 men and women >15 years of age living in the 15 member states of the European Union in 1999. They observed independent associations between leisure-time PA, sitting time, and body mass. More importantly, sedentary time was positively associated with trunk fat, independent of time spent in MVPA. Observational studies report that people who are overweight spend in general 2.5 h/day sitting more than people with normal weight, and they engage in bouts of SB that are of longer duration.[30,72] Conversely, people with normal weight interrupt prolonged sedentary periods with short bouts of PA more often and spend more time in LPA than people who are overweight.[22]

Altogether, these cross-sectional population studies show that people who are less active especially when engaging in active bouts of less than 10 min and who spend more time in sedentary activities are more likely to have higher body weight, BMI, adiposity, and waist circumference. In contrast, active bouts longer than 10 min, independent of the intensity (i.e., LPA or MVPA), are positively associated with less obesity.[69] However, a correlation does not necessarily indicate causality. Do people with overweight or obesity sit more and are less active because of the higher energy cost of moving their heavier body, or do they weigh more because they sit more and are less active? The fact that habitual exercisers are leaner than their inactive counterparts limits the interpretation of causality between PA and body weight and composition. Potential confounding variables such as diet, habitual PA, or maximal aerobic capacity have also rarely been taken into account in these studies. Although observational and epidemiological studies are informative, longitudinal studies provide better evidence regarding causality, and long-term prospective randomized controlled trials (RCTs) provide the best evidence on the relationships between PA and weight.

3.2 | Associations from longitudinal studies

A large number of studies have shown that people who are the most active gain the least weight over time. In 2018, the Physical Activity Guidelines Advisory Committee[73] identified in a literature review 40 studies that assessed the relationship between PA and weight gain in adults over a follow-up period ranging from 1 to 22 years. The authors reported strong evidence supporting relationships between greater amounts of MVPA and attenuated weight gain in adults. A lack of long-term studies however limited evidence to support a dose–response relationship with LPA. Observational studies also report strong relationships between PA and the prevention of long-term weight regain following weight loss. The National Weight Control Registry (NWCR) is the largest prospective investigation of long-term successful weight loss maintenance[74–76] in more than 10,000 people who have lost at least 13.6 kg and have kept the weight off for at least 1 year. Studies from the registry have shown that people who have been successful with weight loss maintenance were people who maintain low EI and performed high levels of PA.[77] Most participants in the NWCR regularly engaged in structured PA[74–76] and self-reported 1 h/day of MVPA,[76] which exceeds the World Health Organization (WHO) physical activity guidelines for adults. Altogether, data from the NWCR support the key role of PA in weight loss maintenance.

More recently, longitudinal studies have examined associations between sedentariness and weight status. The CARDIA study[78] conducted in 1,826 adults (average age of 45.4 years) with overweight or obesity observed that total and prolonged bouts of sedentary time (≥10 min) were directly associated with BMI and waist circumference at baseline. After 5-year of follow-up, only prolonged sedentary bouts at baseline, not total daily sedentary time, were associated with a greater gain in BMI and waist circumference.[78] Results from the Nurses' Health Study cohort (1992–1998)[79] collected in 68,487 women aged between 30 and 55 years showed that each additional 2 h/day spent in TV viewing increased obesity risk by 23% after a 6-year follow-up. Campbell et al.[80] conducted a meta-analysis on 23 prospective cohort studies in adults >18 years from North America and Europe (follow-up ranging from 1 to 21 years). They observed that the most sedentary individuals at baseline had a 1.33-fold higher risk of developing overweight or obesity compared with the least sedentary individuals (mean difference of 8 h/day in SB between both groups). They estimated that an increment of 1 h/day in SB was associated with a significant (but not clinically relevant) 0.02 cm increase in waist circumference over 5 years. Nevertheless, the authors found inconsistent and nonsignificant associations between SB at baseline and other measures of obesity due to a high degree of heterogeneity in the data. Twenty-one studies out of the 23 included in this review used questionnaires to assess SB, which are known to overestimate PA and underestimate SB,[41,81] whereas only two used accelerometry-derived data for assessing daily time spent in SB. To identify the determinants of longitudinal weight gain, a recent clinical trial examined associations between metabolic and behavioral responses to short-term overfeeding and 5-year changes in body mass and composition in adults with normal weight. Individuals who reduced their objectively measured sedentary time the least following a 3-day overfeeding period were those who gained the most body and fat mass over 5 years of observation. Of note, no association was observed between the changes in total calorie intake, TDEE, or daily time spent in MVPA and LPA in response to acute overnutrition and longitudinal weight gain.[82] This finding supports the role of SB in the regulation of body weight and adiposity.

In summary, studies tend to support the idea that greater time spent in SB is associated with weight gain and obesity. But contrary to the consistent associations with MVPA supporting a preventive effect of PA against longitudinal weight gain and regain, there is a lack of prospective large-scale studies and rigorous data to make clear conclusions on the influence of SB on weight changes over time.

3.3 | Interventional studies

3.3.1 | Effect of changes in physical activity and sedentary behaviors on the prevention of unhealthy weight gain

The French ICAPS (Intervention Centered on Adolescents' Physical activity and Sedentary behavior) study[83] aimed to both increase PA and reduce SB in 954 students (aged 11–12 years). This landmark socioecological study relied upon a 4-year multilevel intervention that targeted the physical, organizational (school and city), and social (teachers, peers, and families) living environment of the children and the children themselves through the synergistic actions of multiple partners. Compared to the control schools (no intervention), pupils who received the intervention increased time spent in PA (-0.05 vs. $+0.90$ h/week, respectively), decreased sedentary time (-4.7 vs. -19.9 min/day TV/video viewing, respectively), and gained less weight throughout the 4 year-study ($+0.41$ kg/m^2 vs. $+0.10$ kg/m^2 excess BMI, respectively).[84] Importantly, the lifestyle changes induced by the intervention and the prevention of weight gain were maintained 2.6 years after the end of the intervention with the highest efficacy in the most sedentary and poorest adolescents.[84] In a similar manner, the Dutch FATaintPHAT protocol[85] aimed to assess the efficacy of a computer-tailored program for adolescent students (aged 12–13 years) targeting energy balance-related behaviors (i.e., food intake and PA/SB). This 4-month cluster-randomized trial included 20 schools with a 2-year follow-up. The intervention contributed to developing knowledge of risk behaviors and favored intention toward changing these behaviors. The intervention resulted in lower BMI and waist circumference at the 2-year follow-up in adolescents in the treatment arm compared to those in the control group.[85] The French ICAPS and the Dutch FATaintPHAT both strongly support a role for SB reduction along with an increase in PA for preventing longitudinal weight gain in children and adolescents. To our knowledge, no similar longitudinal study exists in adults or the elderly. Robust data from such studies are needed to support the role of PA in the primary prevention of unhealthy weight in adults.

3.3.2 | Effect of changes in physical activity and sedentary behaviors on weight loss

A general consensus is that exercise training (i.e., MVPA) triggers physiological and behavioral compensatory mechanisms that counteract the exercise-induced energy deficit and lead to only a modest weight loss (1–2 kg).[10] Exercise training is therefore generally not considered to be an effective tool to produce weight loss. Yet, clinically relevant weight loss can be achieved if training is above PA recommendations, or performed under supervision./or performed under supervision.[86–88] In the Midwest Exercise Trial2 (MET 2) study,[89,90] adults with overweight or obesity lost on average 5% of their initial body weight following a 10-month training with an expenditure of 400–600 kcal per supervised exercise session 5 times a week. Nevertheless, high interindividual variability was observed. Interestingly, those who lost weight (i.e., responders, >5% body weight loss) spontaneously decreased time spent in SB during the 10-month intervention in favor of an increase in nonexercise PA (−27 min and + 39 min, respectively); no change was observed in the daily PA patterns of nonresponders (<5% initial body weight). The E-MECHANIC study[91] further showed that low levels of habitual MVPA and activity-related EE are associated with less weight loss during a 24-week exercise intervention in adults with overweight or obesity. In the Step-Up study,[91] an 18-month behavioral weight loss intervention that combined calorie restriction and PA in adults with overweight or obesity (aged 18–55 years) the individuals who lost more than 10% of initial body weight spent more time in prolonged bouts (>10 min) of both MVPA and LPA. Secondary analyses of large intervention studies in adults with overweight or obesity involved in the Diabetes Prevention Program (DPP) or Look AHEAD study also suggested that decreasing SB, particularly of long duration and replacing sedentary time with MVPA, is associated with weight loss.[93] Furthermore, although interventions based on low volumes of exercise training did not produce much weight loss,[94–96] training above the current PA recommendations (225–420 min/week of exercise or MVPA) has shown more success.[97] However, other studies showed that a high volume of additional PA can induce concomitant decreases in nonexercise PA and increases in SB, especially in people with overweight or obesity[98–100] and low levels of habitual PA.[91] The factors triggering the spontaneous behavioral compensations and the associated interindividual variability are however still unclear.

The commonly observed compensatory decreases in LPA in response to high volumes of MVPA may result from the difficulty that sedentary-inactive people encounter when performing unusual and/or new activities of moderate-to-vigorous intensity. For those individuals, increasing LPA may be a reasonable alternative to increase total PA time.[101] Because LPA represents the most variable component of TDEE,[102] it has the potential to influence energy balance and hence, body weight. For example, the study from Holliday et al.[21] compared the effect of two interventions: one targeting LPA through increases in daily PA and another targeting MVPA (5 sessions per week of 30 min/day). The first intervention promoting participation in daily life activities resulted in higher daily time spent in LPA, lower sedentary time, and greater android fat loss after 24 weeks compared to what was observed in the group assigned to the structured MVPA program. Of note, although the time spent in PA of different activities was different between the two groups at the end of the intervention, the total daily active time was not. This study supports the promotion of activities of daily living as an efficient strategy to increase total PA, reduce body mass, and improve adiposity. More recently, Swift et al.[103] observed that the combination of an aerobic exercise protocol with increases in daily steps (to avoid sedentariness) in adults with obesity was more effective than a protocol based on aerobic exercise alone in decreasing waist circumference (−4.7 vs. −2.1 cm, respectively), body weight (−4.1 kg or −3.5% vs. −1.7 kg or −1.8%, respectively) and fat mass (−4.7 vs. −2.6%). Based on these current findings, promoting LPA to decrease sedentariness can be considered a promising strategy to promote weight loss in physically inactive people with overweight or obesity.

Another approach is to target SB in addition to PA.[104,105] Fanning et al.[106] conducted a study of adding structured aerobic exercise of moderate intensity 200 min/week to a dietary weight loss program with or without advice to “sit less” in individuals with obesity (aged 65–85 years) involved in a 6-month supervised protocol. They found that the addition of the structured exercise intervention did not produce more weight loss than the combined weight loss and sit less program, nor the combination of weight loss, sit less, and structured exercise. This finding emphasizes the importance of sitting less before moving more. In a systematic review and meta-analysis including data from 33 studies conducted in adults with normal weight or overweight (BMI 22.1 to 35.9 kg/m^2), Hadgraft et al.[104] reported a small but significant effect of interventions aiming to reduce SB (2 weeks to <6 months) on body weight (−0.56 kg), waist circumference (−0.72 cm), and percent body fat (−0.26%). Another meta-analysis including 18 studies of adults with metabolic disorders such as overweight/obesity or type II diabetes and cardiovascular and musculoskeletal diseases[105] reported that a reduction of 64 min/day in sedentary time was associated with decreased body fat (−0.66%) and waist circumference (−1.52 cm). In another systematic review and meta-analysis of nine studies in adults with both normal weight and overweight (aged 45.3 years), Saeidifard et al.[107] concluded that replacing sedentary time with standing (+1.33 h/day) was associated with reductions in body fat mass (−0.75 kg). These studies show that reducing sedentary time can promote weight loss. Although these effects appear to be minor to moderate at an individual level, they could be beneficial at the population level and therefore be relevant from a public health perspective.

3.3.3 | Effect of changes in physical activity and sedentary behaviors on weight loss maintenance

Although data from the NWCR have identified regular PA, especially of moderate-to-vigorous intensity, as an important tool for long-term weight loss maintenance, RCTs have provided more conflicting results. Several RCTs that examined the effects of increases in PA on weight loss maintenance in adults did not show protective effects of MVPA against weight regain following weight loss.[108–117] By contrast, Fanning et al.[106] found that body and fat mass regains 18 months after the cessation of a 6-month PA intervention were significantly lower in an intervention combining dietary restriction and an exercise program and advised to sit less when compared to the dietary restriction and structured exercise only arm. These differences were linked with greater total active time in the daylong movement intervention due to greater time spent in LPA, confirming the importance of moving throughout the day for weight management. More RCTs with interventions targeting both PA and SB and a tight monitoring of daily activities are needed to better understand the role of PA in weight loss maintenance.

In summary, promoting LPA, instead of or in addition to MVPA, and reducing SB appear to be promising strategies to increase the total volume of PA and induce body weight loss and maintain it over the long term. This seems to be particularly true in sedentary-inactive adults (Box 2).

Box 2. **Effects of changes in physical activity and sedentary behavior on obesity biomarkers**

- The modest effect of exercise training (i.e., moderate-to-vigorous physical activity) on weight loss (1–2 kg lost on average) has been used to argue that physical activity does not play a role in body weight regulation.
- However, the role of physical activity in weight loss maintenance is well accepted.
- Prolonged bouts of sedentary behavior (>30 min) are positively associated with unhealthy weight gain.
- Increasing light intensity physical activity instead of moderate-to-vigorous physical activity may be an easier strategy to implement in daily life of sedentary inactive people with overweight or obesity.
- Cross-sectional and longitudinal studies report beneficial associations between greater physical activity and lower sedentary behavior and measures of obesity and weight gain.
- Well-powered randomized controlled trials are needed to better understand the respective effect of moderate-to-vigorous physical activity, light intensity physical activity and sedentary behavior on body weight regulation.

This is however a new area of research and further studies are needed to better understand the populations that would benefit the most from interventions like this, how sustainable those changes are, and what is the impact on activity EE and TDEE and consequently on body weight and adiposity. As is true for studies on exercise (or MVPA) training, the question of the dose–effect relationship will need to be addressed as well as whether increases in LPA, like increases in MVPA, can elicit compensatory responses that moderate expected effects. Understanding the interactions between the different components of energy balance and the factors regulating those interactions remains complex.

4 | ENERGY BALANCE REGULATION AND BODY WEIGHT

Regardless of the individual predisposition to develop obesity, only a chronic positive energy balance can lead to weight gain. If the concept of energy balance appears to be trivial, it conceals the complexity of the pathophysiology of obesity. Maintaining energy balance is a dynamic process, not a steady state. It is therefore important to investigate the effects of perturbations of one side of the energy balance equation on the other components to understand the behavioral and physiological compensations at play (Box 3). These compensations, volitional or not, have been thoroughly reviewed by King et al.[118] Our intent is not to repeat their work but rather interpret these compensations in the context of changes in SB/LPA versus MVPA and attempt to draw some conclusions on the existence of potential thresholds above which compensations are triggered or not.

4.1 | Effect of changes in physical and sedentary activities on energy expenditure

4.1.1 | In adults with normal weight or overweight

Total daily EE is defined as the sum of resting metabolic rate, diet-induced thermogenesis, and activity-related EE (exercise and volitional activities). Theoretically, an increase in PA should lead to an increase in TDEE. Yet, spontaneous compensatory behavioral and physiological mechanisms seem to be recruited when PA increases.[118] Rowland[8] and Pontzer et al.[9] have argued that an increase in exercise-induced EE is compensated, at least above a certain level, by a decrease in nonexercise-induced EE, thus leading to a plateau in TDEE. When pooling data from the 2,500 adults from the Modeling the Epidemiological Transition Study (METS) cohort,[119] the authors assessed the relationship between TDEE measured with DLW adjusted for sex and anthropometric parameters and PA measured by accelerometry. Analyses showed a change point (i.e., the activity level at which the slope of the change-point regression becomes indistinguishable from zero) around 230 counts per minute per day (CPM/day), which was estimated by the authors to an approximate TDEE of 2,600 kcal/day.[119]

To better understand the impact of increases in PA on TDEE in nonelite athletes, Table 1 summarizes a nonexhaustive list of studies during which free-living TDEE was assessed with the DLW method before and after an exercise protocol intervention. Overall, results reveal a great deal of heterogeneity. Although some studies observed an increase in total EE after an exercise intervention,[90] others did not.[120,121,123] For example, the MET 2 study conducted in adults with overweight or obesity reported increases of 310 kcal/day in TDEE in

TABLE 1 Interventional studies that tested the effects of increases in physical activity on doubly labeled water-derived total daily energy expenditure

Author	Year	Population	Intervention	Changes in total daily energy expenditure	Changes in obesity markers	Differences between group
Goran et al.[120]	1992	6 M (age: 68 [SD 7] years; BMI: 24.9 [2.3] kg/m^2) 5 W (age: 63 [5] years; BMI: 24.0 [3.2] kg/m^2)	8 weeks of endurance training at 60%–85% VO_{2max} No control group	From 2,408 (SD 478) to 2,474 (497) kcal/day	BM: from 71.11 (SD 8.50) to 71.07 (8.41) kg FM: from 21.58 (6.64) to 20.68 (6.61) kg	No significant ↓ BM Significant ↓ FM
Herrmann et al.[90]	2015	31 M/31 W (age: 22.6 [SD 4.2] years; BMI: 31.2 [4.8] kg/m^2)	6 months of aerobic training targeting 400 or 600 kcal/week	Responders[a]: from 2,866 (SD 598) to 3,137 (658) kcal/day	Responders[a]: BM: −8.4 (SD 3.8)%	↓BM: Responders > Nonresponders despite no different changes in energetic outcomes
		Creation of groups a posteriori based on percent weight loss at 10 months[a,b]		Nonresponders[b]: from 3,000 ± 737 to 3,169 ± 675 kcal/day	Nonresponders[b]: BM: −0.04 (2.5)%	
Hunter et al.[121]	2015	$n = 140$ W randomly assigned in one of the three groups Aerobic: (age: 35.2 [SD 7.0] years; BMI: 28.5 [1.5] kg/m^2)	Aerobic: 3–5 times/week during 8 weeks treadmill walking/jogging (20 to 40 min at 67%–80% HR_{max})	Aerobic: from 2,095 (SD 392) to 2,032 (329) kcal/day	Aerobic: BM: from 76.9 (SD 6.7) to 64.4 (6.1) kg FM: from 33.9 (5.0) to 22.0 (4.6) kg (from 44.0 [3.7]% to 33.3 [4.6]%)	↓BM and ↓FM: No difference between the groups
		Resistance: (age: 33.9 [6.1] years; BMI: 28.1 (1.2) kg/m^2)	Resistance: 3–5 times/week during 8 weeks with 1 to 2 sets of 10 reps. at 65% to 80% 1 RM with 2 min rest between sets.	Resistance: from 1,905 (346) to 1,968 (290) kcal/day	Resistance: BM: from 77.5 (7.6) to 65.9 (6.5) kg FM: from 33.7 (5.2) to 21.7 (4.3) kg (from 43.0 [3.6]% to 32.4 [4.5]%)	↓%FM: Resistance > Aerobic and No exercise
		No exercise (age: 35.6 [5.5] years; BMI: 28.2 [1.4] kg/m^2)	All subjects were provided an 800-kcal diet until reach a BMI < 25 kg/m^2	No exercise: from 2,194 (271) to1,953 (388) kcal/day	No exercise: BM: from 78.1 (6.9) to 65.9 (−6.3) kg FM: from 33.4 (4.8) kg to 22.4 (4.5) kg (from 42.7 [3.4]% to 33.5 [4.7]%)	
Wang et al.[122]	2017	Lower dose: 37 W (age: 65.7 [SD 4.5] years; BMI: 25.5 [3.9] kg/m^2)	Walking protocol at 50%–55% $HR_{reserve}$ to achieve 8.0 or 14.0 kJ/kg body weight weekly, respectively	Lower dose: from 2,093 (SD 226) to 2,109 (293) kcal/day	BM: −0.8 (SD 2.1) kg FM: −0.9 (1.8) kg	No significant ↓BM and ↓FM in both groups
		Higher dose: 35 W (age 65.2 [4.1] years; BMI: 25.8 [3.0] kg/m^2)		Higher dose: from 2,056 (307) to 2,126 (383) kcal/day	Results are provided as an average for both groups	

Abbreviations: BM, body mass; FM, fat mass; M, men; SD, standard deviation; W, women.

[a] Responders lost ≥5% of baseline body weight in response to a 10-month supervised exercise training program with verified levels of exercise-induced energy expenditure.

[b] Responders lost <5% of baseline body weight in response to a 10-month supervised exercise training program with verified levels of exercise-induced energy expenditure.

responders (body weight loss of >5% from baseline) after 10 months of supervised exercise 5 days/week with a controlled EE of 400 kcal or 600 kcal per exercise session (2,000 or 3,000 kcal/week).[90] In a 2-month intervention consisting of moderate-intensity aerobic exercise conducted in sedentary men with overweight or obesity, Lefai et al.[100] observed no change in total or activity-related EE due to a spontaneous decrease in nontraining activity-related EE, associated with reduced time spent in LPA. This lack of change is consistent with the constrained TDEE theory[9] as their TDEE may have been close to a threshold value (3,368 kcal/day at baseline). However, in the same study, the authors observed a significant increase in both activity and TDEE in sedentary normal-weight male adults after the same 2-month intervention on PA,[100] with an increase from 2,556 kcal/day at baseline to 2,938 after the intervention. Whybrow et al.[124] observed that young healthy individuals performing 40-min sessions on stationary bicycles targeting 3.3 kcal/kg of body weight for 16 days increased their TDEE to 3,272 kcal/day through exercise-induced EE. However, no change in body or fat mass was observed. In this study, subjects compensated for about 30% of the exercise-induced energy deficit by increasing EI. Nevertheless, a high degree of variability in compensation among individuals was reported by the authors. Indeed, several factors may influence the degree of energy compensation.

Recently, the International Atomic Energy Agency (IAEA) DLW database group combined data of DLW-derived TDEE in 1,754 adults and showed that adiposity has a strong association with the degree of compensation associated with PA through decreases in other components of TDEE.[125] People in the 10th percentile of BMI distribution compensate 27.7% of activity calories versus 49.2% for people in the 90th percentile. In other words, only 72.3% and 50.8% of additional activity-related EE actually translate into extra energy consumed during the day for the 10th and 90th percentiles of BMI, respectively. That means that individuals with higher fat levels compensate more for energy expended in PA than those with lower adiposity. This goes along with the findings of the longitudinal PA intervention study conducted by Lefai et al.[100] and reported above. The recent study by Willis et al.[126] examined the relationship between PA and TDEE objectively measured in 584 older adults (aged 50–74 years) over a 6-month period. Their findings suggest that energy balance status, estimated based on the 6-month changes in body mass, plays an important role in the degree of compensation for energy expended in PA. They showed that TDEE (adjusted on sex and ethnical and anthropometric parameters) increased with deciles of objectively measured PA by 705 and 430 kcal/day between the bottom and top deciles for individuals in stable and positive energy balance (i.e., with stable and higher body mass over 6 months compared to baseline, respectively). No difference was observed in individuals with negative energy balance (i.e., lower body mass over 6 months compared to baseline) given that only a slight decrease of 56 kcal/day was observed between people at the bottom and the top deciles of PA. Goran et al.[120] however observed that elderly people (aged 56–78 years) maintained stable TDEE after an 8-week endurance training intervention at 60%–85% VO_2max (from 2,408 kcal/day at baseline to 2,474 kcal/day after 8 weeks of intervention). No change in body mass or fat mass was observed. The terms (volume, intensity, frequency, and duration) of PA training also seem to influence the impact of PA on TDEE and body weight. Riou et al.[99] compared the effect of 3-month low- versus moderate-intensity exercise training on EI, TDEE, time spent in LPA and SB, and body weight. The two trainings were matched to induce similar extra EE of 1,500 kcal/week. None of the PA interventions impacted EI and TDEE; a nonsignificant decrease in TDEE was observed in the moderate-intensity exercise training group (−173 kcal/day). However, participants in the moderate-intensity training group elicited a greater reduction in daily walking time and a higher increase in time spent lying down than participants in the low-intensity training group. These spontaneous behavioral adaptations indicate more pronounced energy compensation following moderate-intensity training compared to a low-intensity exercise training protocol (161 vs. 49% of the exercise-induced EE). These behavioral and energetic differences translated into about 1 kg weight gain in the moderate-intensity training group versus 1 kg weight loss in the low-intensity training group. Flack et al.[127] recently compared the metabolic effect of a 12-week aerobic training intervention consisting of six sessions per week of 40–60 min at 50%–59% heart rate reserve exercise to a calorie and intensity-matched training program consisting of two sessions per week of 90–120 min exercising in adults with overweight or obesity. Those in the six sessions per week group lost 1.04 kg of body weight and 1.82 kg of fat mass, whereas those in the two sessions per week group maintained stable body and fat mass. Interestingly, individuals in the 6 days/week group expended 85 kcal/day more than their counterparts. The total daily amount of exercise-induced EE may be one of the factors triggering spontaneous behavioral and/or physiological compensations. Nevertheless, interindividual variability is important. For example, Herrmann et al.[90] observed responders and nonresponders in both groups following a 6-month PA intervention targeting either 400 or 600 kcal/day in the MET2 study, with responders losing 8.4% of initial body weight and the nonresponders maintaining initial body weight (−0.04%).

Altogether these studies suggest that 1) increases in PA can raise TDEE above the hypothesized plateau of 2,600 kcal/day proposed by some research groups, at least in response to short-/medium-term interventions; 2) the modalities of PA training likely influence the propensity to compensate for exercise training EE; and 3) the impact of increases in PA on TDEE may depend on individual characteristics, that is, adiposity, habitual EE, age, and energy balance status. An important point that remains unknown is whether the behavioral and physiological compensatory mechanisms develop as people put on weight or whether compensations are a "preexisting" condition as described in the "thrifty gene" theory.[128] In other words, do people accumulate fat mass because they compensate more, or do they compensate more because they have greater adiposity?

4.1.2 | In adults with reduced weight

If the role of PA in weight loss is highly debated, its role in preventing unhealthy weight gain and regain after weight loss is now generally accepted. More recent studies have furthered our understanding of the specific role of PA/SB in weight loss maintenance. In a cross-sectional study, Ostendorf et al.[129,130] observed that people who successfully maintained weight loss (maintaining ≥13.6 kg weight loss for ≥1 year) over the long-term expended more energy than people with normal weight with matched BMI or people with obesity whose BMI was similar to the BMI of the weight loss maintainers prior to weight loss. This greater TDEE was associated with higher activity-related EE and PAL values (1.75 vs. 1.61 vs. 1.55 for the successful weight loss maintainers, individuals with normal weight, and those with obesity, respectively). Furthermore, the weight loss maintainers, like the individuals with normal weight, not only spent more time in LPA and less in SB than people with obesity but also spent more time in MVPA than both other groups. This study suggests that maintaining weight loss over the long term is associated with high levels of both LPA and MVPA and reduced sedentary time. It further supports previous findings indicating that a minimum PAL of 1.7–1.8 is required to prevent excessive weight regain.

In 2003, experts at a consensus meeting were already suggesting that moderate-intensity activity of approximately 45–60 min/day, or 1.7 PAL, was likely sufficient to prevent the transition to overweight or obesity, and 60–90 min of moderate-intensity activity, or 1.8 PAL, were required to prevent weight regain in individuals with former obesity.[14] Regardless of the exact PAL value, it is substantially below the maximal sustainable PAL of 3.5 described by Thurber et al.[12] The same is true for the PAL of the general population (i.e., 1.7–1.8),[13] which is much lower than the hypothetical maximal values. Therefore, the constrained energy model does not exclude a major role of PA in body weight regulation, and future longitudinal studies are needed to clarify the relationships between PA/SB and TDEE. However, focusing our attention on TDEE only, without considering the direct and indirect effects on EI would be misleading. It is only by integrating the effects of PA/SB on both sides of the energy balance equation that we will be able to fully understand their respective effects on the regulation of body mass and composition.

4.2 | Effect of changes in physical and sedentary activities on EI

The study of the relationship between PA and food intake is not new. In the 1950s following observations in Bengali workers, the French–American nutritionist Jean Mayer described that EI was closely coupled with EE at medium to high levels of PA in a "regulated zone." However, at low levels of PA, the coordinated regulation of appetite and energy balance was altered so that EI exceeded requirements and led to weight gain.[131] EI being mediated by appetite signals, various studies suggest a "J-shaped curve" between the whole spectrum of PA (i.e., from very low to very high level) and appetite regulation.[57,131,132] Hedonic and behavioral systems regulating EI may be altered in environments where food is consumed in excess. These dysregulations may overpower biologic systems[133] and amplify the disequilibrium of energy balance.

The concept of "energy flux," defined as "the magnitude of total energy turnover while maintaining energy balance over periods of weeks to months",[11] can help us better understand these different observations. This concept suggests that increasing PA would allow higher EI to balance higher EE in a state of high energy flux. When compared with a state of low energy flux, high energy flux may better regulate weight and fat gain and limit weight regain.[10,11] This approach might be more sustainable than decreasing EI to match low PA over prolonged periods of time. However, the way energy is expended should be considered, rather than just TDEE.[11] Shook et al.[134] conducted a 1-year follow-up in 421 male adults with normal weight. The authors observed higher weight gain in the least active people compared to their most active counterparts. This was partly explained by an incapacity to reduce EI during the period of reduced PA, potentially due to a failure to generate or respond to satiety signals.[135] Although SB should be taken into account in the complex relationship between PA patterns and energy balance, its characterization (i.e., type of SB) should be specifically considered.[136] Cross-sectional population studies have shown associations between time spent in TV viewing or screening and unhealthy diet habits (i.e., higher consumption of energy-dense snacks and sugar-sweetened beverages and less fruit and vegetable consumption) in children and adolescents.[137,138] In an interventional study, Chaput et al.[139] observed that adolescents (average age of 16.7 years) spending 1 h playing video games increased their EE and EI compared with a resting alone condition, resulting in a 163-kcal-positive energy balance. The same research group observed that EE was similar after a "knowledge-based work" task or a control resting condition in 15 healthy adult women (average age of 24.1 years), whereas ad libitum EI increased leading to positive energy balance in the intervention group.[139] Cognitively demanding tasks have been shown to have different physiological consequences and energy sources than physically demanding tasks. This might be explained by a higher glucose demand from the brain and the need to restore glucose homeostasis or an increased stress-induced cortisol secretion.[136] Considering the context in which physical and sedentary activities are performed remains an understudied area and further research is needed. This is particularly important to better understand the overall impact of the technological and digital revolutions that have drastically modified our work and lifestyles.

In contrast to SB, high levels of PA improve homeostatic control of appetite in response to acute disturbances.[140] Stubbs et al.[135] observed that being moderately active provided better regulation of food intake than being sedentary following ad libitum meal, despite no change in hunger, appetite, or weight. Myers et al.[141] reported negative associations between disinhibition and binge eating and both LPA and MVPA (assessed during 1 week in free-living conditions with accelerometers) in people with overweight or obesity. They further observed that the most inactive individuals had higher fat mass and that fat mass was strongly correlated with appetite disorders suggesting a bidirectional relationship between physical inactivity and obesity. Habitual activity seems to further influence the effect of increases in PA. The

E-MECHANIC trial that prescribed structured PA of 8 or 20 kcal/kg of body weight per session during a 24-week intervention in adults with overweight or obesity showed that habitual baseline MVPA levels, not the activity-related EE, predict changes in EI and body weight.[90] In a recent cross-over randomized study,[142] we showed in lean healthy people that prolonged sitting (>30 min) was associated with greater food cravings before a meal compared to a day during which sedentary activities were frequently interrupted by short bouts of moderate-intensity PA, thus indirectly supporting the adverse effect of SB on food intake control.

These studies provide new perspectives on the roles of PA and SB in the regulation of body weight through alterations in appetite regulation. They suggest that while PA likely improves appetite control to match food intake with changing energy requirements, SB likely compromises this homeostatic regulation thus promoting positive energy balance. Importantly, this coupling between PA, appetite, and EI may be primarily influenced by energy flux, but further investigations are needed to better understand the interaction between PA/SB, food intake control, and the regulation of energy balance (Box 3).

Box 3. **Effects of changes in physical activity and sedentary behavior on the components of energy balance**

- High energy flux via high levels of physical activity allows better coupling between energy expenditure and energy intake than low energy flux.
- Control of appetite and energy intake is dysregulated in inactive and sedentary individuals compared to physically active people.
- Increases in physical activity, especially in moderate-to-vigorous physical activity, can trigger spontaneous behavioral and/or physiological compensatory responses that diminish the impact of physical activity-related energy expenditure on total daily energy expenditure and/or induce increases in energy intake.
- A large interindividual variability exists in the effects of physical activity on total daily energy expenditure and body weight.
- Changes in total daily energy expenditure in response to increases in physical activity are influenced by body weight status, adiposity, energy balance status, age, and exercise modality.
- Increasing light intensity physial activity and decreasing sedentary behavior, instead of increasing moderate-to-vigorous physical activity, may elicit less energy compensation, and therefore lead to greater increases in total daily energy expenditure and energy deficit.

Some studies suggest that food intake may be determined by lean body mass,[143,144] especially under energy deficit conditions during which the restoration of fat-free mass may become a priority for the body. Others have shown that 24-h EE is the major determinant of EI.[145,146] Despite heterogeneity in protocol modalities (e.g., type of exercise, duration and intensity, and chronicity), other data argue in favor of a beneficial effect of PA on the appetite through hormone secretion in order to reach the targeted "reference" weight.[147] For example, Martins et al.[148] observed an improvement in appetite control following 6 weeks of moderate exercise training in 29 healthy sedentary adults. King et al.[149] found that the increased fasting hunger following a 12-week exercise protocol in men and women with overweight and obesity was accompanied by increased satiation following a fixed meal, partially explained by an increase in anorexigenic hormone release, such as glucagon-like peptide 1 (GLP1). Flack et al.[127] reported in participants with overweight or obesity that greater reductions in postprandial leptin concentration following a 12-week exercise intervention were associated with lower energy compensation (difference between estimated and actual changes in body composition). The authors suggested that reductions in the levels of postprandial leptin indicate an improvement in leptin sensitivity with exercise training which helps to control food intake. During a 2-month bedrest study,[150] a model that induces extreme levels of physical inactivity and sedentariness, we observed that lean healthy active women were able to adjust their EI to the very low levels of PA and that fasting leptin was negatively associated with spontaneous EI, thus also suggesting some relationships between PA, leptin, and food intake. The mechanisms underlying the relationships between PA and food intake still warrant further investigations though.

4.3 | The protective effects of physical activity against overfeeding

It has been suggested that overfeeding might trigger adaptive physiological responses to dissipate excess energy in order to achieve energy balance and maintain a stable weight by increasing TDEE. Levine et al.[20] observed that following 8 weeks of overnutrition in adults with normal weight, those that spontaneously increased their PA the most gained the least amount of body fat. An early study by Ravussin et al.[151] found an increase in TDEE following 9 days of overfeeding of which one-third was explained by increased basal metabolic rate. However, only 25% of the excess energy consumed was dissipated through an increased EE, the other portion being stored in the body. More recently, Johannsen et al.[152] conducted a longer overfeeding protocol (8 weeks) and found a significant increase in TDEE driven by an increase in sleeping metabolic rate. Even if this increase was statistically significant, from a clinical point of view, it was insufficient to prevent weight gain. Long-term overfeeding studies described an increase in body weight that was slowing down as the intervention was sustained over several

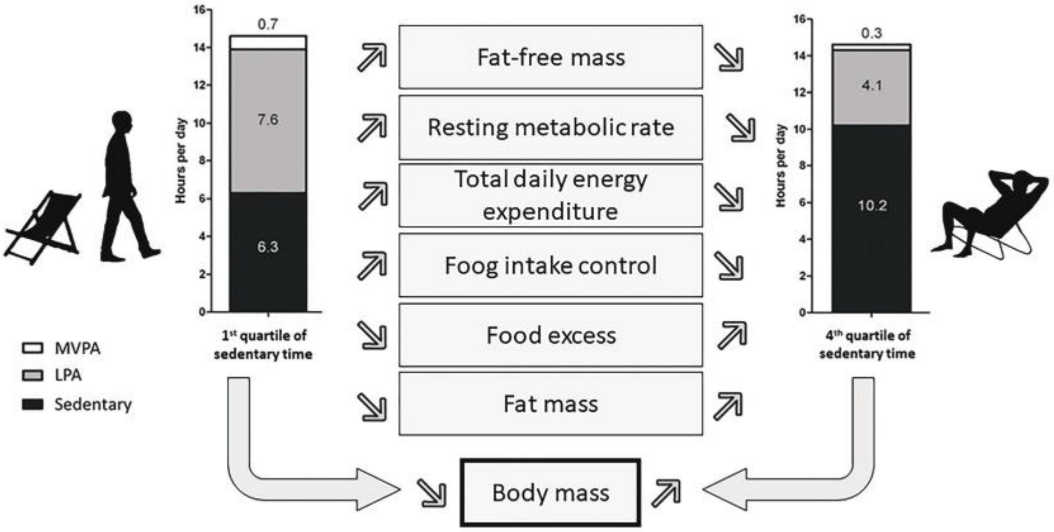

FIGURE 3 Schematic representation of the effects of sedentary behaviors on the components of energy balance and, hence, body weight regulation. Using the data of Owen et al,[154] the left side of the figure represents a nonsedentary person (10th percentile of total daily sedentary time), whereas the right side of the figure represents a highly sedentary person (90th percentile of total daily sedentary time). LPA, light physical activity; MVPA, moderate-to-vigorous physical activity

months, likely due to increases in both resting metabolic rate and energy costs to move a heavier body.[153] None of these studies observed increasing levels of PA thought to be protective against weight gain like it was initially suggested in the study by Levine et al.[20] Finally, the existence and magnitude of these adaptations are still debated[152] in part due to the large interindividual variability observed in these studies.[153] Results suggest that the dynamic processes that maintain the stability of energy balance over time (i.e., simultaneous increase or decrease in EE with increases or decreases in EI) are complex and need further investigation (Figure 3).

5 | EFFECT OF PHYSICAL ACTIVITY AND SEDENTARINESS ON NUTRIENT OXIDATIVE BALANCE

In addition to a stable energy balance, a second condition is required for the maintenance of a stable body weight: stable oxidative balances. This means the amounts of substrates consumed by the body need to be oxidized. As elegantly explained by the two-compartment model of Jean-Pierre Flatt,[155] oxidative balance is influenced by the capacity to store each macronutrient in the body. Proteins are required for the structure, function, and regulation of the body's tissues and organs, and their balance is tightly regulated by the organism. Because the storage of carbohydrates (CHO) is limited to a few hundred grams essentially in skeletal muscles and the liver, changes in CHO intakes induce large variations in the level of the glycogen stores, which are rapidly adjusted by their oxidation. Conversely, changes in fat intake cause only small variations in the level of the large stores of fat in the body and are not followed by equivalent changes in lipid oxidation. Fat balance has been shown to be tightly linked to energy balance and plays an important role in body mass and composition management.[156]

By lowering glycogen stores, exercise can promote fat oxidation.[156] By contrast, low levels of PA reduce the ability of the body to use lipids as substrates for meeting energy needs[157] and promote the development of metabolic inflexibility (i.e., incapacity for an organism to adjust fuel oxidation to changes in fuel availability[158,159]). The concept of metabolic flexibility implies that metabolic health is determined by the ability to adapt to conditions of temporary stress, such as overfeeding or exercise, and thus maintain or regain homeostasis. Previous studies have shown that activity-related EE, but not TDEE, predicts nutrient partitioning[160] and metabolic flexibility.[161–163] Importantly, these associations between activity-related EE, nutrient partitioning, and metabolic flexibility were observed independent of detectable changes in energy balance and even in the absence of an increase in TDEE.[100] Finally, it has been shown that the inability to both decrease time spent sedentary and adjust fuel use (metabolic inflexibility) to an acute overfeeding episode was correlated with long-term weight gain.[82,164] Altogether, these studies suggest key roles for PA, SB, and activity-related EE in the regulation of oxidative balance and metabolic flexibility, two key factors involved in the regulation of body weight[163] (Box 4).

Box 4. **Effects of changes in physical activity and sedentry behavior on nutrient metabolism and metabolic flexibility**

- Low levels of physical activity reduce the ability of the body to use lipids as substrates for meeting energy needs.
- High levels of daily physical activity and sedentary behavior are respectively positively and negatively associated with the ability of the body to adjust substrate use to changes in nutrient availability (i.e., metabolic flexibility).

6 | CONCLUSION AND FUTURE DIRECTIONS

Despite decades of research, the epidemic of obesity is still growing worldwide likely because the causes of weight gain are still debated. The role of PA in body weight regulation has been greatly questioned recently. However, a large body of data show that high volumes of PA and limited sedentariness are associated with lower body weight, lower rates of weight gain, lower rates of obesity, and less regain following weight loss. High levels of PA also contribute to improving body composition, metabolic parameters and appetite control, which are key determinants of energy balance, and hence body weight regulation. However, promoting MVPA is often associated with compensatory increases in sedentariness and EI and decreases in nonexercise EE, which counteract the beneficial impact of MVPA on TDEE at least in people at-risk for or with overweight and obesity and/or with low habitual PA. These physiological and behavioral compensations reduce the beneficial effects of MVPA in the treatment of unhealthy weight gain. Recent data show that promoting LPA along with reducing SB are promising alternative/complementary strategies to increase total daily PA and EE that may not trigger spontaneous energy compensations to the same degree as MVPA. These findings support a role for PA/SB in body weight regulation, especially when viewed from a public health perspective. The recent research focuses on MVPA in the treatment of obesity and the study of the effects of very high levels of PA on TDEE have provided useful insights into our understanding of the regulation of TDEE and the role that compensatory responses play in moderating the effects of a PA intervention. However, the dominance of these ideas may have overshadowed the important role that promoting PA could play in improving human health in our current environment. From a public health perspective, promoting PA, especially LPA, along with reducing/fragmenting SB may be important strategies to combat the obesity epidemic. Further studies are however needed to provide rigorous and robust data to support this message and develop practical strategies to increase PA and prevent SB at the population level.

From a broader perspective, a potential reason for our failure at combatting the obesity epidemic is that the complex interactions between biological, behavioral, and socioecological factors and their respective role in the regulation of body weight are still not well understood. Our view is that as long as PA is above a certain threshold level, diet, genes, and other factors play a role, but their contribution is less pronounced. To address this complexity, future research will need to:

- consider and objectively measure daily LPA and SB;
- consider that the role of PA in the primary prevention of weight gain may differ from its role in the prevention of weight regain after weight loss. In the context of weight gain, PA is an environmental factor that contributes to inducing a positive energy balance when low levels of PA are not matched by low levels of EI. Following weight loss, PA is now rather a tool to combat the biological mechanisms that are driving weight regain. The role of PA in these two distinct biological contexts requires specific research; yet, studies on people who have lost weight are still missing;
- dissociate PA and PA-related EE. Although these two are closely related, PA refers to behaviors and body movements, and PA-related EE corresponds to the metabolic cost associated with PA. Measuring PA-related EE objectively requires combining the DLW method and indirect calorimetry. Raw data (i.e., unadjusted) of PA-related EE should no longer be presented as it is prone to misinterpretation. Although an adult with overweight can have PA-related EE as high as an adult with normal weight, the former results from the high cost of moving a large body, whereas the latter is explained by high levels of daily PA. Data adjusted for body mass/composition should be presented in the future.
- conduct adequately powered RCTs to examine the influence of PA/SB on weight regulation. These studies should consider potential confounding variables such as habitual PA, maximal aerobic capacity, the type of PA and SB performed, and the context in which the physical and sedentary behaviors are undertaken, food intake habits, sleep pattern, sex, etc.;
- consider interdisciplinary approaches that will aim to determine the relative contribution of the environmental, socioecological, and biological factors in body weight regulation. As we recently discussed it in a viewpoint,[37] studying populations that have maintained a preindustrial lifestyle and are facing rapid and drastic environmental changes due to modernization may help reach this goal.

In conclusion, rigorous research is still needed to fully understand the role of physical activities (i.e., MVPA, LPA, and SB) in the regulation of body weight, and to develop efficient and easy-to-implement strategies for improving obesity management.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Pierre BOURDIER

Régulation de la balance énergétique en conditions environnementales extrêmes : inférence sur la régulation du poids chez l'humain

Résumé

La conquête de nouveaux horizons étant le propre l'humanité, elle a imposé aux individus de repousser leurs limites en s'acclimatant aux contraintes de l'environnement, jusqu'à certaines limites. La nutrition inadaptée aux besoins énergétiques en condition extrême est une de ces limites et impose aux participants de considérer la régulation de la balance énergétique comme une priorité. Cette thèse a pour objectif de quantifier objectivement les besoins énergétiques des individus en conditions environnementales extrêmes, ainsi que les changements de composition corporelle associés. Si la régulation de cette balance s'adapte aux perturbations légères grâce à la mise en place de mécanismes compensatoires, les résultats des modèles extrêmes utilisé dans ce travail de thèse montrent les limites de cette régulation en dehors d'un certain niveau d'activité physique dues à un découplage entre les apports et les dépenses énergétiques. Or, la capacité à maintenir une balance énergétique négative sur le long terme reste méconnue en raison de la nature diverse des compensations pouvant être stimulées, de la nature du déficit ou encore des caractéristiques individuelles des participants.

Mots clé| activité physique | balance énergétique | composition corporelle | environnement extrême

Summary

The conquest of new horizons being the own of humanity, it compelled to individuals to push away their limits by acclimatize to the constraints of the environment, at least until certain limits. The mismatch between nutrition and energy requirements in extreme environment is one of these limits, and compels individuals to consider energy balance regulation as a priority. This thesis aims to objectively quantify individuals' energy requirements in extreme conditions, and the associated body composition changes. While the regulation of energy balance is effective to face light disturbances on one component or another because of compensatory mechanisms, results from extreme models used in the present thesis show the limits of this regulation outside a certain range of physical activity level, mostly because of a mismatch between energy intakes and expenditures. However, the capacity to sustain a negative energy balance during prolonged period is poorly known, partly because of the broad range of compensatory mechanisms at play, but also the nature of the deficit or individuals' characteristics.

Keywords | physical activity | energy balance | body composition | extreme environment