Age but not menopausal status is linked to lower resting energy expenditure

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Abstract

Background/Objectives

Uncertainty remains whether ageing before late adulthood and menopause reduce fat-free mass and fat mass–adjusted resting energy expenditure (REE_{adj}). We therefore investigated whether REE_{adj} differs 1) between middle-aged and younger women and 2) in middle-age by menopause status. We repeated the age group comparison between middle-aged mothers and their daughters to partially control for genotype. We also explored whether oestradiol and follicle-stimulating hormone concentrations or body fat percentage explain REE_{adj} in midlife.

Subjects/Methods

We divided 120 women, including 16 mother–daughter pairs, into age groups. Group I (n=26) consisted of participants aged 17–21, group II (n=35) aged 22–38 and group III (n=59) aged 41–58 years. Group III women were pre- or perimenopausal (n=19), postmenopausal (n=30) or postmenopausal hormone therapy users (n=10). REE was assessed using indirect calorimetry, body composition using dual-energy X-ray absorptiometry and hormones using immunoassays.

Results

Group I had 126 kcal/d (95% confidence interval [CI], 93–160; P<0.001) higher REE_{adj} than group III, while group II had 88 kcal/d (CI, 49–127; P<0.001) higher REE_{adj}. Furthermore, the daughters had 100 kcal/d (CI, 63–138; P<0.001) higher REE_{adj} than their mothers. In group III, REE_{adj} did not differ by menopause status, but body fat percentage was positively associated with REE_{adj} (β=0.39, P=0.003).

Conclusions

We demonstrated that REE declines with age in women before late adulthood, even when controlling for body composition and partially for genetic background, and that menopause does not contribute to the decline in REE_{adj}. Menopause-associated fat accumulation may actually elevate REE_{adj}.

INTRODUCTION

Energy expenditure is often assumed to begin declining in early to middle adulthood, but Pontzer et al. (1) challenged this assumption by showing that fat-free mass (FFM) and fat mass (FM)-adjusted total energy expenditure (TEE_{adj}) were stable between the ages of 20 and 63. However, they found that similarly adjusted resting energy expenditure (REE_{adj}) stabilises at adult levels at age 18 and declines from age 46 onwards, although the limited numbers of middle-aged participants with a measured REE prevented the authors from making definitive inferences about the onset of REE_{adj} decline, leading to a conclusion that age affects neither TEE_{adj} nor REE_{adj} in adults before the age of ~60 (1). Nevertheless, previous studies are consistent with an earlier turning point for REE_{adj} (2–4), and we therefore sought to assess whether REE_{adj} declines before old age. Our dataset also included mother–daughter dyads, some of which had TEE measured with doubly labelled water, enabling us to partly control the analyses for genetic background and to explore whether increasing age showed similar associations with TEE_{adj} as it does with REE_{adj}.

Like ageing, menopause is widely believed to reduce REE_{adj}, and the topic has broad interest because many women gain FM during the menopausal transition (5,6) and associate the change in body composition with slowing metabolism. During the menopausal transition, ovarian follicular activity ceases, causing a striking shift in women's sex hormone profile. The decline in systemic oestradiol (E2) concentration in particular is thought to

decrease REE_{adj}, potentially via both central (7) and peripheral (8) mechanisms, while the increase in follicle-stimulating hormone (FSH) secretion may also play a role (9,10). Menopausal hormone therapy (MHT) can restore E2 and decrease FSH levels, which should reverse the potential menopause-associated decline in REE_{adj}. However, whether menopause truly decreases REE_{adj} is still uncertain because longitudinal studies following women over the menopausal transition (11,12), cross-sectional studies comparing women with different menopausal states (13–16) and MHT interventions (15,17–19) have been inconclusive. Therefore, in addition to investigating whether REE_{adj} differs between young and middle-aged women, we also assessed whether REE_{adj} differs between middle-aged women with different menopause statuses. We restricted the menopause analysis to middle-aged participants to limit the confounding effects of age. We also explored whether serum E2 and FSH concentrations or body fat percentage explain REE_{adj} in midlife.

METHODS

Participants

The participants were 120 women who had taken part in one of four studies performed at the Faculty of Sport and Health Sciences of the University of Jyväskylä (**Fig. 1**). They were healthy and did not take medication affecting metabolism, although hormonal contraception and MHT use were allowed.

The Calex study (data collection 2008–2011) investigated whether lifestyle factors influence muscle and adipose tissues (20). The current study used that data, which was taken from 17 middle-aged and 21 younger women, including 16 mother–daughter pairs; ten pairs also had their TEEs measured. The data has been partly used in an earlier validation study (21). The EsmiRs study (Estrogen and microRNAs as Modulators of Women's

Metabolism, 2019–2020) examined resting and exercise metabolism in middle-aged women (22), and we included all 42 participants with measured REEs from that study. The Physique study (2019, Isola et al. unpublished) investigated the effects of competition weight loss in normal-weight participants as earlier (23); here, we used the baseline data from 23 young women collected before their weight loss. Finally, the Athletic Performance and Nutrition study (NO RED-S, 2021, Ihalainen et al. unpublished) studied the health of winter sports athletes at the beginning of their training and competition seasons; from that study, we used baseline data from 17 young women, measured during the transition season when their training load was the lowest.

*****Figure 1*****

Age categorisation

We used age as a continuous explanatory variable and categorised the participants into three age groups. REE_{adj} plateaued at age 18.0 (95% confidence interval [CI], 16.8–19.2) and started to decline at age 46.5 (CI, 40.6–52.4), while TEE_{adj} plateaued at 20.5 (CI, 19.8–21.2) and started to decline at 63.0 years (CI, 60.1–65.9) (1). We therefore assigned participants aged 18~21 years to group I, 22~39 years to group II and 40~60 years to group III.

Menopausal status and sex hormone concentrations

Group I and II participants were naturally menstruating women (group I, n = 12; group II, n = 20) or hormonal contraception users (group I, n = 14; group II, n = 15). We determined the menopausal status of group III women with the Stages of Reproductive Aging Workshop (STRAW) + 10 guidelines (24) using menstrual and serum FSH data: 11 were premenopausal

(PRE), eight were perimenopausal (PERI), 30 were postmenopausal (POST) and ten were postmenopausal MHT users (MHT). We combined the PRE and PERI women into a PRE/PERI group to represent women with meaningful ovarian E2 production but performed a sensitivity analysis without the PERI women because E2 levels decline in perimenopause. All the MHT group women used E2 alone (n = 1) or with a progestogen (n = 9). The administration was oral in seven cases and transdermal in three.

Fasting serum E2 concentrations were measured for all participants, except seven young women in the Calex study, and FSH concentrations were measured for group III participants using enzyme-amplified chemiluminescence immunoassays (IMMULITE 1000 or 2000 XPi, Siemens Medical Solution Diagnostics, Los Angeles, CA, USA). The serum was separated according to standard procedures and stored at −80°C. Details concerning menopausal status, hormone concentration assessments and the use of hormonal products are in **Supplementary Information**.

Body composition

Body composition was assessed with dual-energy X-ray absorptiometry (DXA Prodigy, GE Lunar Corp., Madison, WI, USA). We calculated the appendicular lean mass index (ALMI) by scaling appendicular lean mass (kg) to height (m) squared.

Resting and total energy expenditure

REE was measured in all studies using the same Vmax Encore 92 metabolic cart (Sensormedics, Yorba Linda, CA, USA) and ventilated hood in the same thermoneutral laboratory; the cart was calibrated accordingly before each measurement. The REE

assessment details are in **Supplementary Information**. Measurements were performed in the morning after overnight fasting, with resting periods of 0–30 min and measurement periods of 15–30 min. We excluded at least the first 5 min of measurement data; for all participants, we located a steady-state period of at least 5 min during which the coefficient of variation was 10% or less for $\dot{V}O_2$ and $\dot{V}CO_2$, and we calculated REE with the modified Weir equation (25). We made REE comparable between different-sized participants using residuals—the differences between measured and predicted values—from a linear regression model:

$$\text{REE (kcal/d)} = 413.4 + 20.2 \times \text{FFM (kg)} + 1.7 \times \text{FM (kg)}$$

Herein, we refer to residual REE as REE_{adj}. We also built three alternative explanatory models (**Table S1**): the first included age as a covariate with FFM and FM; to the second we added ALMI; and in the third, the study data collection period.

To assess TEE in the Calex study, the overnight fasting participants gave a urine sample and ingested a doubly labelled water dose of 1 g per kg of body mass (21). A second urine sample was collected after 4–6 h, and a third 14 days later. The samples were analysed in triplicate using mass spectrometry (Metabolic Solutions Inc., Merrimack, NH, USA) at the University of Alabama. TEE was calculated as in Schoeller et al. (26).

Statistical analyses

We performed the statistical analyses using R 4.2.1 (27), and the code is available in https://doi.org/10.5281/zenodo.7446075. We report descriptive statistics as means with standard deviations or as medians with first and third quartiles, but we did not test group differences in order to preserve statistical power. We verified the model's assumptions before accepting the results and used an alpha level of 0.05 for statistical significance.

We estimated the association between age and REE_{adj} and compared the measured REE and REE_{adj} between the age groups with linear mixed-effect models using the *nlme* package (28), with family identification as a random effect. We also performed a sensitivity analysis using FFM, FM and ALMI-adjusted REE as the outcome. For the mother–daughter pairs, we first compared the REE_{adj} and then TEE using the measured TEE as the outcome and FFM and FM as covariates. We estimated intraclass correlation coefficients using the *psych* package (29) with one-way random-effects models—intraclass correlation compares within- and between-pair variations, thereby expressing how strongly the mothers and daughters resemble each other. Last, we used linear regression to compare the measured REE and REE_{adj} between the menopause groups and to estimate the association between the sex hormone concentrations or body fat percentage and REE_{adj}, with and without age adjustment. E2 was ln-transformed to meet model assumptions.

RESULTS

Participant characteristics

Table 1 shows participant characteristics and energy expenditures across age and menopause groups, and **Table S2** shows the same in the mother–daughter pairs. Based on the descriptive statistics, group II women had higher FFM and lower FM, and in group III, sex hormone concentrations varied between the menopause groups, as expected.

*****Table 1*****

Age and energy expenditure

FFM and FM explained 47% of the REE variance, while the inclusion of age increased the adjusted R^2 to 68%; neither the ALMI nor information on the study data collection period improved the explanatory value. **Table S1** presents the full results, and **Fig. S1** shows scatterplots between the predicted and measured REE values.

Age was inversely associated with REE_{adj} (**Fig. 2B**). Group I had 140 kcal/d (CI, 82–199) higher measured REE and 126 kcal/d (CI, 93–160) higher REE_{adj} (**Fig. 2A**) than group III, while group II had 187 kcal/d (CI, 133–240) higher measured REE and 88 kcal/d (CI, 49–127) higher REE_{adj} ($P < 0.001$ for all). The group differences in the FFM, FM and ALMI-adjusted REE were slightly smaller (**Table S3**).

In the 16 mother–daughter pairs, the daughters had 100 kcal/d (CI, 63–138; $P < 0.001$) higher REE_{adj} than their mothers (**Fig. 2C**). In the ten pairs with REE and TEE measurements, the daughters had 85 kcal/d (CI, 45–125; $P = 0.003$) higher REE_{adj} than their mothers, but there was no significant difference in TEE_{adj} ($B = 26$ kcal/d; CI, -128–180; $P = 0.75$, **Fig. 2D**). Intraclass correlation coefficients were 0.05 (CI, -0.43–0.52; $P = 0.42$) for REE_{adj}, 0.83 (CI, 0.49–0.96; $P < 0.001$) for TEE and 0.92 (CI, 0.71–0.98; $P < 0.001$) for TEE_{adj} (**Fig. S2**).

*****Figure 2*****

Resting energy expenditure in midlife

Compared with the POST group, the measured REE was not significantly different in either the PRE/PERI ($B = 46$ kcal/d; CI, -26–119; $P = 0.21$) or MHT groups ($B = -27$ kcal/d; CI, -118–63; $P = 0.55$); neither was REE_{adj} (PRE/PERI; $B = 7$ kcal/d; CI, -42–55; $P = 0.78$; MHT: $B = -31$ kcal/d; CI, -91–30; $P = 0.31$, **Fig 3A**). A sensitivity analysis without PERI women did not alter the results. Consequently, we did not adjust the models further for age. Body fat

percentage—but not the E2 (**Fig. 3C**) or FSH concentrations (**Fig. 3D**)—was positively associated with REE_{adj} (**Fig. 3B**), especially when also adjusted for age (**Table 2**).

*****Figure 3*****

*****Table 2*****

DISCUSSION

Ageing through adulthood and menopause are thought to slow basal metabolism, potentially predisposing women to obesity. This study demonstrates that increasing age is associated with a decline in REE among young and middle-aged women, even after adjusting for body composition and partly controlling for genetic background. However, menopause did not contribute to the age-associated decline in REE_{adj}. Furthermore, unlike sex hormone status, higher body fat percentage was related to higher REE_{adj} in middle-aged women.

The decline in age-associated REE_{adj} aligns with previous cross-sectional studies in which the decline began around 35~47 years of age (1,3,4). The turning point for REE_{adj} therefore likely occurs before 60 years of age (1), but whether the phenomenon represents an actual slowing of cellular metabolism remains unclear. Low metabolic rate organs contribute more to FFM as we age (30), but ageing also causes tissue quality changes; for example, the brain grey–white matter ratio (31) and skeletal muscle density (32) decline from young to middle adulthood, meaning that each kilogramme of the brain or muscle tissue has fewer metabolically active cells as ageing proceeds. Current body composition assessment methods, like DXA, cannot detect such changes (30), so FFM adjustments that assume FFM composition and quality are constant may overestimate the age-associated decline in $REE_{adj.}$ Indeed, Roubenoff et al. (33) found no association between age and FFM-adjusted REE when

assessing FFM using total body potassium analysis, which directly estimates cell mass. If slowing cellular metabolism contributes to the observed decline in REE_{adj}, it may result from altered systemic hormone and cytokine stimulation (30), with intrinsic changes in hormone responsiveness, protein synthesis, maintenance of membrane potentials and mitochondrial function (34). We also compared the TEE_{adj} of middle-aged mothers and their daughters and found that they were very similar, despite differences in their REE_{adj}. This finding confirms that TEE is highly heritable (35) but also suggests that the age-associated decline in REE_{adj} may have a negligible effect on TEE before late adulthood (1).

Our finding that menopausal status or sex hormone concentrations did not explain REE_{adj} in midlife broadly agrees with previous studies. Long-term ovarian hormone suppression studies in premenopausal women have shown some yet not fully convincing evidence of a REE_{adj} decline (36,37), while MHT has no apparent effect on REE in post-menopause (15,17,18). Observational evidence suggests that menopause has a negligible impact on REE_{adj}. Lovejoy et al. (11) found that sleeping energy expenditure and TEE_{adj} decreased in women transitioning from pre-menopause to post-menopause during a four-year follow-up, but the changes were no different from participants who remained premenopausal, which suggests that the decreases were related to ageing, not menopause. Furthermore, the menopausal transition was not associated with REE in the longitudinal MONET study (12), and cross-sectional studies have shown no association between menopausal status and measured REE (14,16), FFM-adjusted REE (13,15) or FFM-adjusted TEE (38), while a study that did show a higher REE in MHT users than non-users (14) failed to adjust the analyses for differing tissue masses. Finally, the REE_{adj} and TEE_{adj} trajectories did not differ between middle-aged women and men in a study by Pontzer et al. (1).

The lack of a clear association between menopause and REE_{adj} is unexpected because the cessation of reproductive functions should decrease basal metabolism. There are

at least three potential explanations; first, with the limitations of body composition assessment and indirect calorimetry methods (30), the energy expenditure of female reproductive processes may be so small relative to other functions contributing to REE that its loss is difficult to detect. The second explanation is that the effects of menopause cannot be disentangled from the effects of ageing, especially because ageing progresses differently between individuals, although this is insufficient to explain why MHT interventions do not increase REE (15,17,19). The third, more speculative explanation is that women reallocate energy during menopause from reproduction to other purposes; Hazda hunter-gatherer women, for example, increase the time spent on gathering resources for their offspring (39), potentially reallocating the freed energy to movement and maintenance of the locomotor system (40). Women in industrialised nations live differently and may therefore use the energy to build energy reserves and bodily defence mechanisms, reallocating the freed energy inside the REE component (40). Increased FM, especially to the trunk, may further promote metabolic deterioration (41), inflammation (42) and sympathetic nervous system activity (43), thereby further elevating the REE (44–47). Indeed, we found that, instead of sex hormone concentrations, a higher body fat percentage was associated with higher REE_{adj} in midlife. Such trade-offs could explain why women's REE_{adj} does not decline and their cardiometabolic risk profile worsens after menopause in industrialised societies (48).

Finally, it should be mentioned that a decrease in absolute REE following skeletal muscle loss could also contribute to menopause-associated FM accumulation if women do not match the drop by reducing energy intake. We previously reported that a peri- to postmenopausal transition during an ~14-month follow-up period resulted in a 0.2 kg lean mass loss, likely from skeletal muscle (49); but, assuming that the mass-specific metabolic rate of skeletal muscle is 13 kcal/d at rest (50), the loss would reduce REE by 2.6 kcal/d,

which cannot explain the 0.8 kg increase in FM (6), especially as the tissue changes happen gradually.

The main limitations of this study are its cross-sectional and secondary nature. We pooled existing studies to generate a sufficiently large sample and cannot entirely exclude a clustering effect. Considering the impact of sex hormones, we did not control for the use of hormonal products or menstrual cycle phases. Furthermore, serum E2 concentrations were analysed with immunoassays, whose accuracy is limited for the low E2 levels seen post-menopause.

CONCLUSIONS

REE_{adj} declines in women from young to middle adulthood, likely due to ageing rather than menopause, but whether falling cellular metabolic rates contribute is unclear. Current evidence does not support the inference that menopause reduces REE_{adj}. Menopause-associated FM accumulation may even elevate REE_{adj} in midlife. Longitudinal data from middle-aged women with differing sex hormone trajectories are needed to reconcile whether menopause truly affects REE in a meaningful way.

DATA AVAILABILITY: The dataset cannot be made publicly available for legislative reasons but can be made available upon reasonable request addressed to principal investigators of each substudy: Calex (CS, EKL), EsmiRs (EKL, doi.10.17011/jyx/dataset/83491), Physique (JPA) and NO RED-S (JKI).

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AUTHOR CONTRIBUTIONS: JEK performed EsmiRs study measurements, gave guidance for the Physique and NO RED-S studies, analysed data, and wrote the manuscript. EKL led and designed the EsmiRs study with the help of JEK, H-KJ, MH, UMK, and JL. PW performed measurements and gave guidance for the EsmiRs study. SC led and designed the Calex study with help from PW. JPA and JH led and designed the Physique study with the help of VI, who also participated in data collection. JKI led, designed, and collected data in the NO RED-S study with the help of EKA. All authors revised the manuscript and approved its final version.

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ETHICAL APPROVAL: Studies were conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Central Finland Health Care District (Calex; memo 22/8/2008 and 5/2009, EsmiRs; 9U/2018, Physique; 19U/2018) or the Ethics Committee of the University of Jyväskylä (NO RED-S 514/13.00.04.00/2021). Participants gave informed consent.

COMPETING INTERESTS: The authors declare no competing interests.

REFERENCES

1. Pontzer H, Yamada Y, Sagayama H, Ainslie PN, Andersen LF, Anderson LJ, et al. Daily energy expenditure through the human life course. Science. 2021 Aug 13;373(6556):808–12.

2. Müller MJ, Bosy-Westphal A, Klaus S, Kreymann G, Lührmann PM, Neuhäuser-Berthold M, et al. World Health Organization equations have shortcomings for predicting resting energy expenditure in persons from a modern, affluent population: generation of a new reference standard from a retrospective analysis of a German database of resting energy expenditure. Am J Clin Nutr. 2004 Nov;80(5):1379–90.

3. Geisler C, Braun W, Pourhassan M, Schweitzer L, Glüer CC, Bosy-Westphal A, et al. Gender-Specific Associations in Age-Related Changes in Resting Energy Expenditure (REE) and MRI Measured Body Composition in Healthy Caucasians. J Gerontol A Biol Sci Med Sci. 2016 Jul;71(7):941–6.

4. Siervo M, Oggioni C, Lara J, Celis-Morales C, Mathers JC, Battezzati A, et al. Age-related changes in resting energy expenditure in normal weight, overweight and obese men and women. Maturitas. 2015 Apr;80(4):406–13.

5. Greendale GA, Sternfeld B, Huang M, Han W, Karvonen-Gutierrez C, Ruppert K, et al. Changes in body composition and weight during the menopause transition. JCI Insight. 2019 Mar 7;4(5).

6. Juppi HK, Sipilä S, Fachada V, Hyvärinen M, Cronin N, Aukee P, et al. Total and regional body adiposity increases during menopause-evidence from a follow-up study. Aging Cell. 2022 Jun;21(6):e13621.

7. Xu Y, López M. Central regulation of energy metabolism by estrogens. Mol Metab. 2018 Sep;15:104–15.

8. Klinge CM. Estrogenic control of mitochondrial function. Redox Biol. 2020 Apr;31:101435.

9. Liu P, Ji Y, Yuen T, Rendina-Ruedy E, DeMambro VE, Dhawan S, et al. Blocking FSH induces thermogenic adipose tissue and reduces body fat. Nature. 2017 Jun 1;546(7656):107–12.

10. Mattick LJ, Bea JW, Singh L, Hovey KM, Banack HR, Wactawski-Wende J, et al. Serum Follicle-Stimulating Hormone and 5-Year Change in Adiposity in Healthy Postmenopausal Women. J Clin Endocrinol Metab. 2022 Jul 14;107(8):e3455–62.

11. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond). 2008 Jun;32(6):949–58.

12. Duval K, Prud’homme D, Rabasa-Lhoret R, Strychar I, Brochu M, Lavoie JM, et al. Effects of the menopausal transition on energy expenditure: a MONET Group Study. Eur J Clin Nutr. 2013 Apr;67(4):407–11.

13. Hodson L, Harnden K, Banerjee R, Real B, Marinou K, Karpe F, et al. Lower resting and total energy expenditure in postmenopausal compared with premenopausal women matched for abdominal obesity. J Nutr Sci. 2014 Feb 13;3:e3.

14. Monda V, Salerno M, Fiorenzo M, Villano I, Viggiano A, Sessa F, et al. Role of Sex Hormones in the Control of Vegetative and Metabolic Functions of Middle-Aged Women. Front Physiol. 2017;8:773.

15. Bessesen DH, Cox-York KA, Hernandez TL, Erickson CB, Wang H, Jackman MR, et al. Postprandial triglycerides and adipose tissue storage of dietary fatty acids: impact of menopause and estradiol. Obesity (Silver Spring). 2015 Jan;23(1):145–53.

16. Gould LM, Gordon AN, Cabre HE, Hoyle AT, Ryan ED, Hackney AC, et al. Metabolic effects of menopause: a cross-sectional characterization of body composition and exercise metabolism. Menopause. 2022 Feb 28;29(4):377–89.

17. Marlatt KL, Lovre D, Beyl RA, Tate CR, Hayes EK, Burant CF, et al. Effect of conjugated estrogens and bazedoxifene on glucose, energy and lipid metabolism in obese postmenopausal women. Eur J Endocrinol. 2020 Oct;183(4):439–52.

18. Anderson EJ, Lavoie HB, Strauss CC, Hubbard JL, Sharpless JL, Hall JE. Body composition and energy balance: lack of effect of short-term hormone replacement in postmenopausal women. Metabolism. 2001 Mar;50(3):265–9.

19. Lwin R, Darnell B, Oster R, Lawrence J, Foster J, Azziz R, et al. Effect of oral estrogen on substrate utilization in postmenopausal women. Fertil Steril. 2008 Oct;90(4):1275–8.

20. Ojanen X, Cheng R, Törmäkangas T, Rappaport N, Wilmanski T, Wu N, et al. Towards early risk biomarkers: serum metabolic signature in childhood predicts cardio-metabolic risk in adulthood. EBioMedicine. 2021 Oct;72:103611.

21. Yu Z, Völgyi E, Wang R, Ember A, Wiklund P, Alén M, et al. Comparison of heart rate monitoring with indirect calorimetry for energy expenditure evaluation. Journal of Sport and Health Science. 2012 Dec 1;1(3):178–83.

22. Karppinen JE, Juppi HK, Hintikka J, Wiklund P, Haapala EA, Hyvärinen M, et al. Associations of resting and peak fat oxidation with sex hormone profile and blood glucose control in middle-aged women. Nutr Metab Cardiovasc Dis. 2022 Sep;32(9):2157–67.

23. Hulmi JJ, Isola V, Suonpää M, Järvinen NJ, Kokkonen M, Wennerström A, et al. The Effects of Intensive Weight Reduction on Body Composition and Serum Hormones in Female Fitness Competitors. Front Physiol. 2016;7:689.

24. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. Menopause. 2012 Apr;19(4):387–95.

25. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. 1949. Nutrition. 1990 Jun;6(3):213–21.

26. Schoeller DA, Ravussin E, Schutz Y, Acheson KJ, Baertschi P, Jéquier E. Energy expenditure by doubly labeled water: validation in humans and proposed calculation. Am J Physiol. 1986 May;250(5 Pt 2):R823-830.

27. R Core Team. R: A language and environment for statistical computing. 2022.

28. Pinheiro J, Bates D, DebRoy S, Deepayan S, Heisterkamp S, Van Willigen B, et al. nlme: Linear and Nonlinear Mixed Effects Models. 2022. Available from: https://CRAN.R-project.org/package=nlme

29. Revelle W. psych: Procedures for Psychological, Psychometric, and Personality Research. 2022. Available from: https://CRAN.R-project.org/package=psych

30. Müller MJ, Geisler C, Hübers M, Pourhassan M, Braun W, Bosy-Westphal A. Normalizing resting energy expenditure across the life course in humans: challenges and hopes. Eur J Clin Nutr. 2018 May;72(5):628–37.

31. Giorgio A, Santelli L, Tomassini V, Bosnell R, Smith S, Stefano ND, et al. Age-related changes in grey and white matter structure throughout adulthood. Neuroimage. 2010 Jul 7;51(3–2):943.

32. Lauretani F, Bandinelli S, Bartali B, Iorio AD, Giacomini V, Corsi AM, et al. Axonal degeneration affects muscle density in older men and women. Neurobiology of Aging. 2006 Aug 1;27(8):1145–54.

33. Roubenoff R, Hughes VA, Dallal GE, Nelson ME, Morganti C, Kehayias JJ, et al. The effect of gender and body composition method on the apparent decline in lean mass-adjusted resting metabolic rate with age. J Gerontol A Biol Sci Med Sci. 2000 Dec;55(12):M757-760.

34. Heymsfield SB, Smith B, Dahle J, Kennedy S, Fearnbach N, Thomas DM, et al. Resting Energy Expenditure: From Cellular to Whole-Body Level, a Mechanistic Historical Perspective. Obesity (Silver Spring). 2021 Mar;29(3):500–11.

35. Joosen AMCP, Gielen M, Vlietinck R, Westerterp KR. Genetic analysis of physical activity in twins. Am J Clin Nutr. 2005 Dec;82(6):1253–9.

36. Melanson EL, Gavin KM, Shea KL, Wolfe P, Wierman ME, Schwartz RS, et al. Regulation of energy expenditure by estradiol in premenopausal women. J Appl Physiol (1985). 2015 Nov 1;119(9):975–81.

37. Gavin KM, Melanson EL, Hildreth KL, Gibbons E, Bessesen DH, Kohrt WM. A Randomized Controlled Trial of Ovarian Suppression in Premenopausal Women: No Change in Free-Living Energy Expenditure. Obesity (Silver Spring). 2020 Nov;28(11):2125–33.

38. Tooze JA, Schoeller DA, Subar AF, Kipnis V, Schatzkin A, Troiano RP. Total daily energy expenditure among middle-aged men and women: the OPEN Study. Am J Clin Nutr. 2007 Aug;86(2):382–7.

39. Hawkes K, O'Connell JF, Blurton Jones NG. Hadza Women's Time Allocation, Offspring Provisioning, and the Evolution of Long Postmenopausal Life Spans. Current Anthropology. 1997;38(4):551–77.

40. Lieberman DE, Kistner TM, Richard D, Lee IM, Baggish AL. The active grandparent hypothesis: Physical activity and the evolution of extended human healthspans and lifespans. Proc Natl Acad Sci U S A. 2021 Dec 14;118(50):e2107621118.

41. Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. Am J Epidemiol. 1997 Apr 1;145(7):614–9.

42. Timpson NJ, Nordestgaard BG, Harbord RM, Zacho J, Frayling TM, Tybjærg-Hansen A, et al. C-reactive protein levels and body mass index: elucidating direction of causation through reciprocal Mendelian randomization. Int J Obes (Lond). 2011 Feb;35(2):300–8.

43. Scherrer U, Randin D, Tappy L, Vollenweider P, Jéquier E, Nicod P. Body fat and sympathetic nerve activity in healthy subjects. Circulation. 1994 Jun;89(6):2634–40.

44. Geisler C, Braun W, Pourhassan M, Schweitzer L, Glüer CC, Bosy-Westphal A, et al. Age-Dependent Changes in Resting Energy Expenditure (REE): Insights from Detailed Body Composition Analysis in Normal and Overweight Healthy Caucasians. Nutrients. 2016 Jun 1;8(6):E322.

45. Bosy-Westphal A, Wolf A, Bührens F, Hitze B, Czech N, Mönig H, et al. Familial influences and obesity-associated metabolic risk factors contribute to the variation in resting energy expenditure: the Kiel Obesity Prevention Study. Am J Clin Nutr. 2008 Jun;87(6):1695–701.

46. Calton EK, Pathak K, Soares MJ, Alfonso H, Keane KN, Newsholme P, et al. Vitamin D status and insulin sensitivity are novel predictors of resting metabolic rate: a cross-sectional analysis in Australian adults. Eur J Nutr. 2016 Sep;55(6):2075–80.

47. Soares MJ, Zhao Y, Calton EK, Pathak K. Triglycerides and systolic blood pressure negatively mediate the direct relationship of vitamin D status to resting energy expenditure: A cross sectional analysis. Diabetes Metab Syndr. 2022 Nov 9;16(12):102664.

48. Maas AHEM, Rosano G, Cifkova R, Chieffo A, van Dijken D, Hamoda H, et al. Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists. Eur Heart J. 2021 Mar 7;42(10):967–84.

49. Juppi HK, Sipilä S, Cronin NJ, Karvinen S, Karppinen JE, Tammelin TH, et al. Role of Menopausal Transition and Physical Activity in Loss of Lean and Muscle Mass: A Follow-Up Study in Middle-Aged Finnish Women. J Clin Med. 2020 May 23;9(5):E1588.

50. Elia M. Organ and Tissue Contribution to Metabolic Rate. In: Energy Metabolism: Tissue Determinants and Cellular Corollaries. New York: Raven Press; 1992. p. 61–79.

Table 1. Participant characteristics and energy expenditures according to age and menopause groups

	Age groups (*N* = 120)			Menopause groups (*n* = 59)		
	I	**II**	**III**	**PRE/PERI**	**MHT**	**POST**
Variable	***n* = 26**	***n* = 35**	***n* = 59**	***n* = 19**	***n* = 10**	***n* = 30**
Age, y	19.8 (1.1)	28.2 (4.3)	53.8 (3.5)	50.7 (4.3)	55.1 (1.7)	55.3 (1.9)
Sex hormone concentrations						
E2, nmol/l	0.10 (0.03–0.20)[#]	0.17 (0.06–0.41)	0.14 (0.08–0.33)	0.29 (0.18–0.55)	0.29 (0.17–0.38)	0.09 (0.06–0.12)
FSH, IU/l				8 (7–25)	38 (34–61)	80 (71–102)
Anthropometrics						
Height, cm	165.6 (5.6)	165.3 (5.8)	166.4 (5.0)	168.1 (4.6)	166.5 (5.6)	165.3 (4.8)
Total mass, kg	65.0 (10.5)	64.5 (7.9)	68.5 (9.1)	69.1 (9.0)	71.3 (12.3)	67.1 (7.9)
Body mass index, kg/m^2	23.7 (3.5)	23.6 (2.0)	24.7 (3.1)	24.5 (3.2)	25.7 (4.2)	24.5 (2.7)
Fat-free mass, kg	44.2 (5.0)	49.8 (5.3)	44.2 (4.2)	45.6 (4.1)	43.4 (4.2)	43.6 (4.1)
Fat mass, kg	20.9 (8.2)	14.7 (5.8)	24.2 (7.3)	23.6 (7.8)	27.9 (8.4)	23.4 (6.4)
Lean mass, kg	41.6 (4.7)	47.2 (5.1)	41.7 (4.0)	42.9 (3.9)	40.8 (4.1)	41.1 (4.0)
Appendicular lean mass, kg	18.5 (2.6)	21.8 (2.7)	17.9 (1.9)	18.4 (2.0)	17.6 (1.9)	17.6 (1.9)
Appendicular lean mass index	6.7 (0.7)	8.0 (0.8)	6.5 (0.6)	6.5 (0.5)	6.4 (0.6)	6.4 (0.6)
Body fat percentage, %	31 (8)	23 (7)	36 (7)	35 (8)	40 (5)	36 (6)
Resting energy expenditure						
Measured, kcal/d	1,430 (110)	1,474 (146)	1,286 (124)	1,323 (105)	1,249 (143)	1,276 (128)
Predicted$_{\text{FFM \& FM}}$, kcal/d	1,339 (104)	1,442 (107)	1,345 (87)	1,372 (84)	1,335 (98)	1,332 (85)
Predicted$_{\text{FFM, FM \& age}}$, kcal/d	1,440 (103)	1,467 (94)	1,286 (92)	1,322 (86)	1,283 (115)	1,264 (84)
Total energy expenditure	***n* = 10**		***n* = 10**			
Measured, kcal/d	2,162 (310)		2,148 (236)			

Data as means (standard deviation) or medians (interquartile range), [#] *n* = 19

E2, oestradiol; FFM, fat-free mass; FM, fat mass; FSH, follicle-stimulating hormone, MHT, menopausal hormone therapy; PRE/PERI, pre- or perimenopause; POST, postmenopause

Table 2. The associations between age, serum sex hormone concentrations, and body fat percentage with fat-free mass and fat mass-adjusted resting energy expenditure in midlife (n = 59)

Model	**Age**		**Age, E2**		**Age, FSH**		**Age, Body fat %**	
	Std beta	*P*-value	Std beta	*P*-value	Std beta	*P*-value	Std beta	*P*-value
Intercept	378.2	0.018	342.7	0.055	398.6	0.022	240.2	0.103
Age, y	-0.350	0.007	-0.312	0.041	-0.370	0.011	-0.388	0.001
log(E2)			0.068	0.652				
FSH, IU/l					0.045	0.751		
Body fat percentage, %							0.421	< 0.001
R^2/adjusted R^2	0.12/0.11		0.13/0.09		0.12/0.09		0.30/0.27	

E2, oestradiol; FSH, follicle-stimulating hormone; Std, standardised

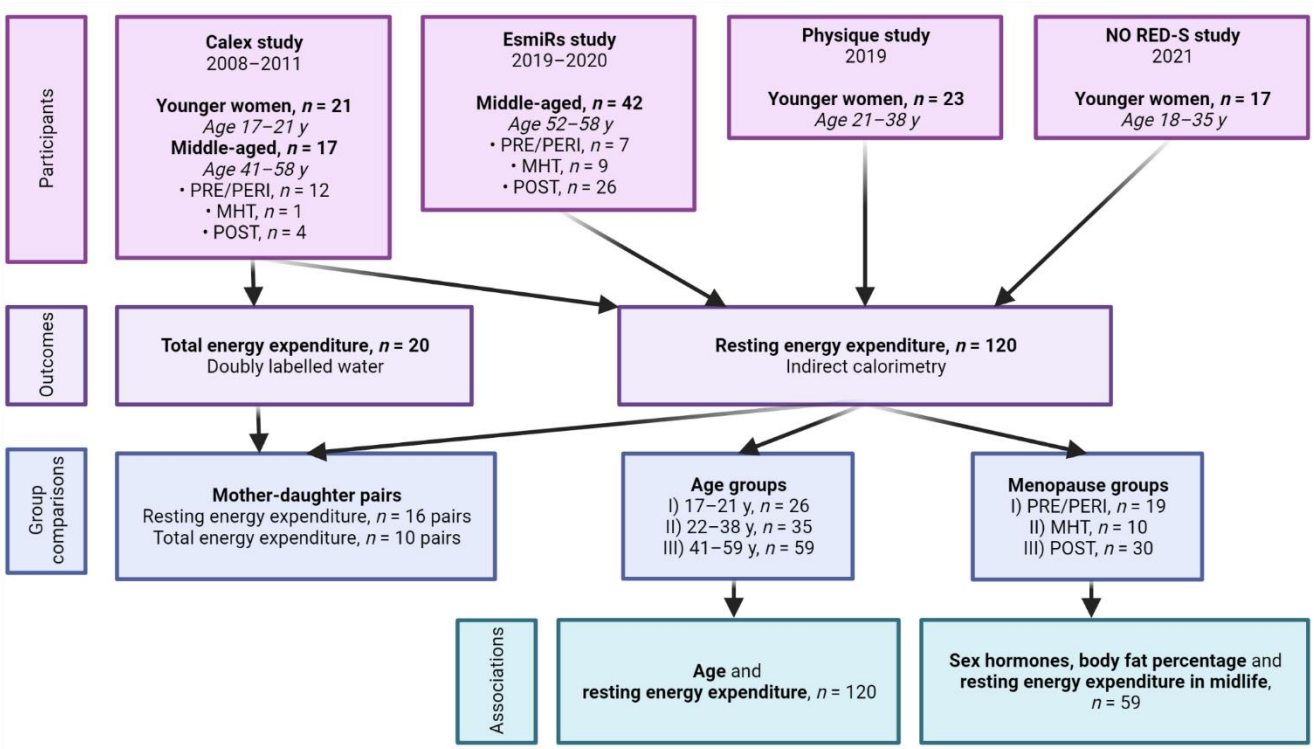

Figure 1. Description of the study participants, outcomes, and statistical approaches.

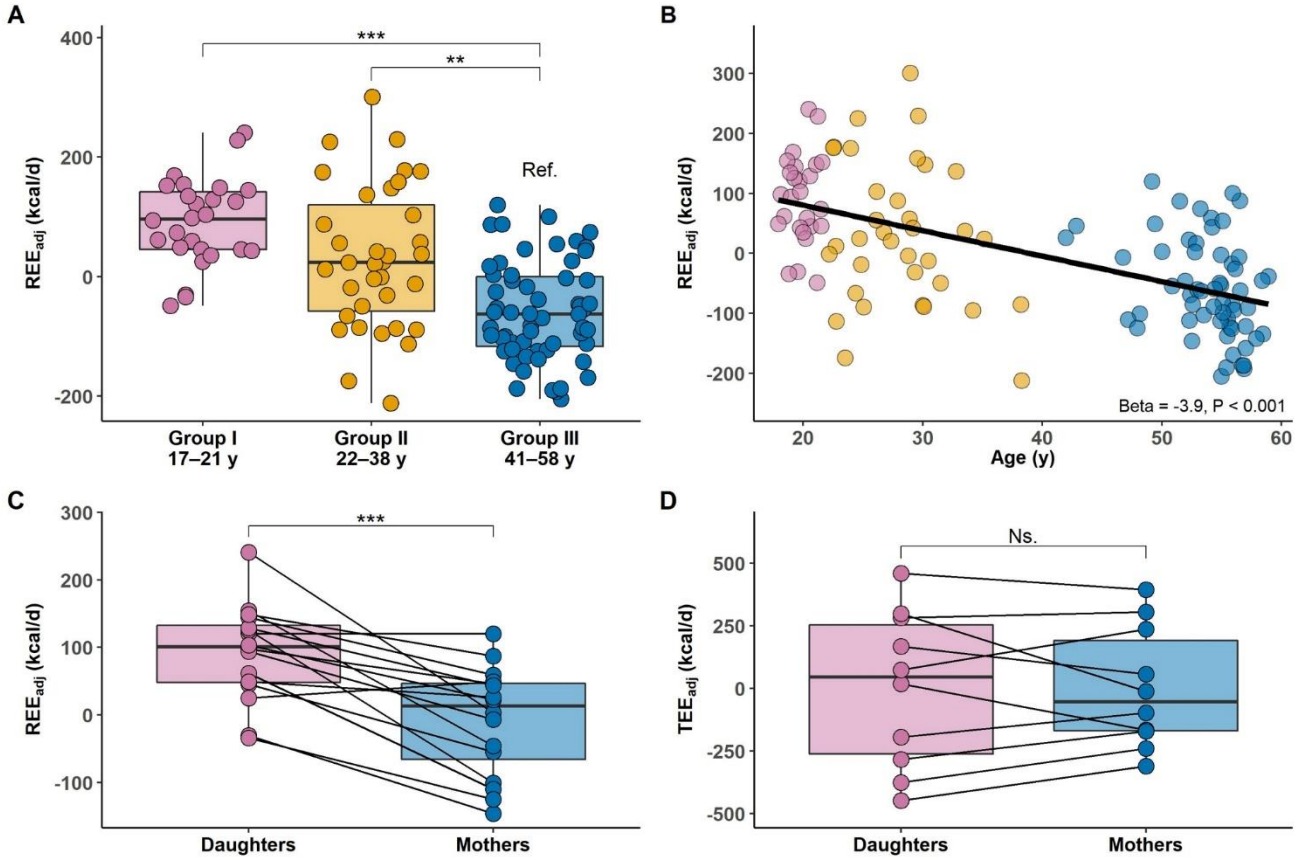

Figure 2. A) Fat-free mass and fat mass adjusted resting energy expenditure (REE_{adj}) across age groups, B) the association between age and REE_{adj}, and C) REE_{adj} and D) TEE_{adj} in the mother-daughter pairs. Boxplots show group means with standard deviations and whiskers, 1.5 × interquartile ranges.

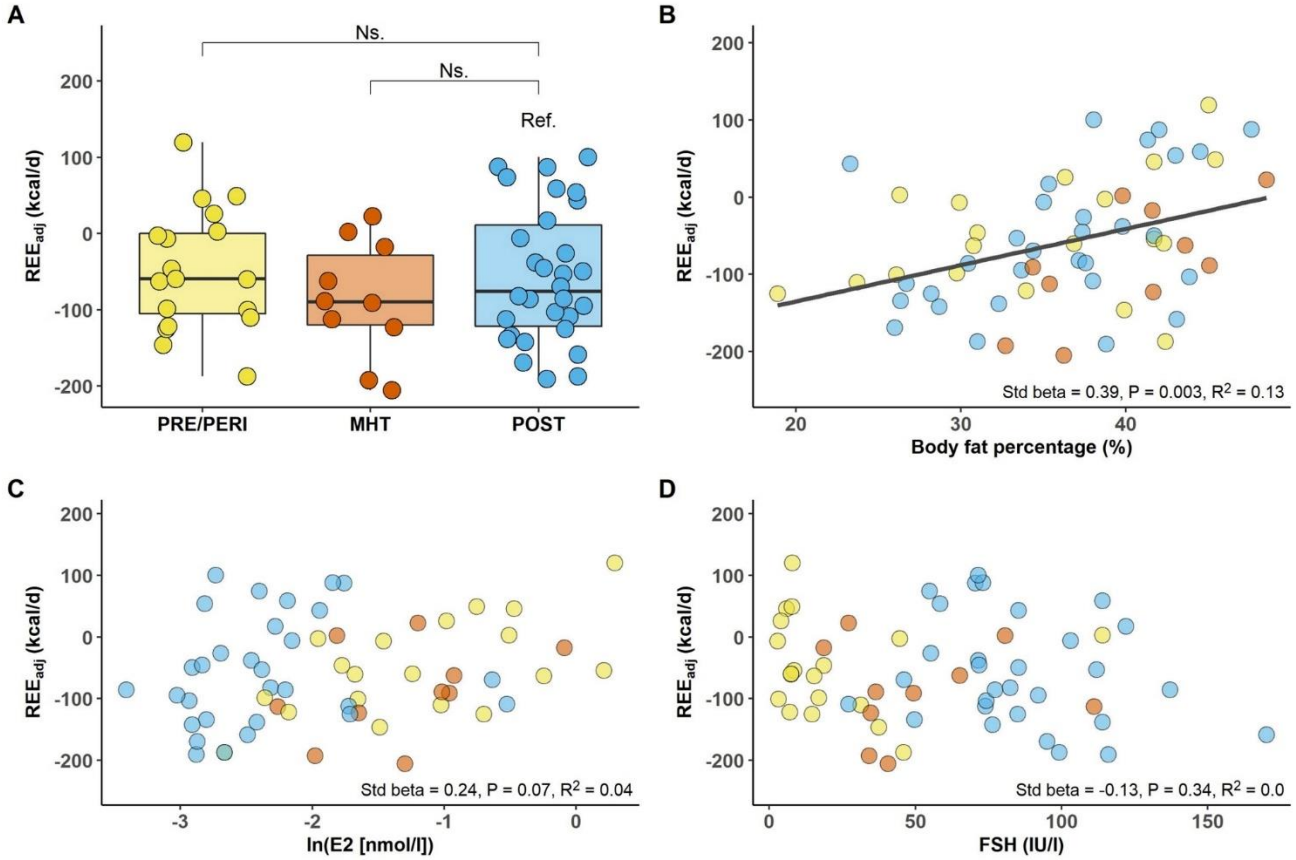

Figure 3. Fat-free mass and fat mass adjusted resting energy expenditure (REE_{adj}) in midlife (n = 59) A) by menopause groups, and the associations between B) body fat percentage, C) oestradiol (E2), and D) follicle-stimulating hormone (FSH) and adjusted REE_{adj}. Boxplots show group means with standard deviations and whiskers, 1.5 × interquartile ranges.