SUPPLEMENTARY MATERIALS

Supplementary Methods

Expanded description of Statistical Analyses

First, we modelled the association between physical activity patterns and incident endometrial cancer using Cox proportional hazard models. Letting ($e_{i1},\ldots,e_{i5}$) denote the binary variables encoding LTPA with e_{i1} representing the inactive group, x_i denote BMI in midlife[i], and ($z_{i1},\ldots,z_{ip}$) denote covariates, we assumed the following model:

$$\log(HR_i) \propto \sum_{j=2}^{5} \beta_{Ej}^{1} e_{ij} + \beta_X^1 x_i + \sum_{j=1}^{p} \beta_{Zj}^{1} z_{ij} \qquad (1)$$

Note, the superscripts on the β will differentiate the coefficients for the three types of models (i.e., exposure/outcome, exposure/mediator, mediator/outcome). Second, we modeled the association between long-term LTPA and midlife BMI using multinomial logistic regression, with the midlife BMI outcome categorized as normal weight (<25.0 kg/m^2), overweight (25.0–29.9 0 kg/m^2), obese class I (30.0–34.9 0 kg/m^2), obese class II (35.0–39.9 0 kg/m^2), and obese class III (≥40.0 0 kg/m^2).. Letting ($M_{i1},\ldots,M_{i4}$) denote the binary variables encoding midlife BMI with M_{i1} representing the normal weight group and letting $OR_{ij} = P(M_{ij} = 1)/P(M_{i1} = 1)$ with P denoting the probability of the event, we assumed the following set of models

$$\log\left(OR_{ij}\right) \propto \sum_{j=2}^{5} \beta_{Ej}^{2} e_{ij} + \beta_X^2 x_i + \sum_{j=1}^{p} \beta_{Zj}^{2} z_{ij} \qquad (2)$$

Third, we modeled the association between midlife BMI (i.e., same categories as above) and endometrial cancer using Cox proportional hazard models. We considered models with and without LPTA:

$$\log(HR_i) \propto \sum_{j=2}^{4} \beta_{Mj}^{3} M_{ij} + \beta_X^3 x_i + \sum_{j=1}^{p} \beta_{Zj}^{3} z_{ij} \qquad (3)$$

$$\log(HR_i) \propto \sum_{j=2}^{4} \beta_{Mj}^{4} M_{ij} + \beta_X^4 x_i + \sum_{j=1}^{p} \beta_{Zj}^{4} z_{ij} + \sum_{j=2}^{5} \beta_{Ej}^{4} e_{ij} \qquad (4)$$

We then explored the relationship between long-term LTPA, midlife obesity and endometrial cancer using the mediation framework proposed by Lange et al.[30] Here, the "total" effect of LTPA on endometrial cancer can be decomposed into an "indirect" effect mediated by midlife BMI and a "direct" effect (see Figure 1). For performing the mediation analysis, we consider each of the four non-reference LTPA categories separately, i.e., maintain low, maintain high, increasers, and decreasers (e.g., we perform four analyses; each analysis considers only the subset of the cohort in the reference or target LPTA category). Using standard counterfactual notation[30], let $T_i(e_{ij}, M_i(e_{ij}^*))$ denote an individual's survival time (i.e., time until cancer) if the exposure is set to e_{ij} and the mediator, M, is set to the value it would have taken had the exposure been set to e_{ij}^*. Then, we assume the log-hazard can be modeled as

$$\log\left(P\left(T_i = t \middle| T_i \geq t, e_{ij}, M_i(e_{ij}^*)\right)\right) \propto \beta_0 + \beta_{ej} e_{ij} + \beta_{e^*j} e_{ij}^* + \beta_x x_i + \sum_{j=1}^{p} \beta_{zj} z_{ij} \qquad (5)$$

We define the natural indirect effect (HR_I) by exp (β_{e^*j}), the natural direct effect (HR_D) by exp (β_{ej}), and the proportion mediated $\beta_{e^*j}/(\beta_{e^*j} + \beta_{ej})$; we estimate these quantities and their 95% confidence intervals using the simulation approach developed by Lange[30] with the simulation model defined by equation (4).

Supplementary Tables

Supplementary Table 1. Baseline characteristic for analytical sample and full cohort.

Demographic/Behavior Characteristics	Not included in the study[a]	Analytical sample	Diff (in %)[b]
Total No.	59,631	67,705	
Mean age (SD), y	63.0 (5.4)	62.3 (5.5)	-1.1
Non-Hispanic White, No. (%)	52,985 (88.9)	62,688 (92.6)	3.7
Less than high school, No. (%)	4.058 (6.8)	2,625 (3.9)	-3.0
Smoker: >20 cig/day, No. (%)	2,231 (3.7)	2,439 (3.6)	-0.1
LTPA at age group			
Mean (SD), h/wk			
15-18 y	4.0 (2.8)	4.0 (2.8)	0.0
19-29 y	4.2 (2.8)	4.1 (2.7)	-0.1
35-39 y	4.1 (2.7)	4.1 (2.6)	-0.1
40-61 y	3.5 (2.7)	3.7 (2.7)	0.0
BMI, No. (%)			
At 18 y ≥ 30.0 kg/m^2	802 (1.3)	1,005 (1.5)	0.2
Current ≥ 30.0 kg/m^2	13,382 (22.4)	14109 (20.8)	-1.6
Healthy Eating Index, Men (SD), 0-100[c]	68.9 (9.4)	69.2 (9.3)	0.4
Energy intake, Mean (SD), kcal/day[d]	1.6 (0.8)	1.6 (0.7)	0.0
Alcohol, Mean (SD), g/d	5.7 (18.4)	6.6 (17.9)	15.8
Nulliparous, No. (%)	7,416 (12.4)	12,103 (17.9)	5.5
Use of oral contraceptives - never, No. (%)	36,161 (60.6)	39,533 (58.4)	-2.2
Menopausal hormone therapy use – Estrogen only, No. (%)	5,772 (9.7)	4,249 (6.3)	-3.4

[a]Includes women that responded to the Risk Factor Questionnaire and whose questionnaires were not completed by proxies and did not have a diagnosis of cancer. BMI = body mass index; LTPA = leisure time physical activity

[b]Computed as the percent difference between the analytical sample and original cohort.

[c]2015 HEI scores range from 0 (least healthy) to a 100 (most healthy) and describe diet quality as recommended by the 2015-2020 Dietary Guidelines for Americans.

[d]Indicates kcal/day per 1000.

Supplementary Table 2. Odds of long-term leisure time physical activity (LTPA) pattern assignment by BMI classification at age 18 years[a].

	Odds of long-term LTPA pattern assignment[b], OR (95% CI)[c]			
BMI at age 18yrs	Maintain low (n=11,125)	Maintain high (n=21,843)	Increasers (n=13,469)	Decreasers (n=15,707)
Overweight/Obese (BMI ≥ 25.0 kg/m^2)	0.60 (0.49, 0.74)	0.37 (0.30, 0.46)	0.64 (0.52, 0.79)	0.43 (0.35, 0.53)
Normal weight (BMI < 25.0 kg/m^2)	Referent	Referent	Referent	Referent

[a]Participants with little or no physical activity (<1 hr/wk) at each age period were classified as Inactive; those maintaining low levels of activity over time were classified as Maintaining low activity; those maintaining high levels of activity over time were classified as Maintaining high activity; those that increased their activity over time were classified as Increasers; and those that decreased their activity over time were classified as Decreasers. BMI = body mass index; OR = odds ratio; CI = confidence interval

[b]The odds that an overweight/obese participant would be assigned to a given long-term leisure time physical activity (LTPA) pattern, as compared to the inactive pattern. For example, to calculate the first set of values (0.60 [0.49, 0.74]), we limited the population to individuals with either the inactive or maintain-low pattern, and then performed logistic regression with LTPA pattern as the dependent variable and overweight/obese status as the independent variable.

[c]Odds ratios were adjusted for: age (years), race-ethnicity (Non-Hispanic white, Non-Hispanic black, Hispanic, Other or missing), education (less than high school, high school, post high-school or some college, Bachelor degree or more, missing), smoking status/dose (never smoker, former smoker and ≤20 cigarettes/day, former smoker and >20 cigarettes/day, current smoker and ≤20 cigarettes/day, current smoker and > 20 cigarettes/day, missing), diet quality (2015 Healthy Eating Index; 0–100 points), total energy intake (kcal/day), alcohol consumption (grams/day), parity (number of births), use of oral contraceptives (never or <1 year, 1–4 years, 5–9 years, ≥10 years, missing), and menopausal hormone therapy use (never, continuous estrogen plus progestin (EPT) use [15+ days progestin/month], sequential EPT [<15 days progestin/month], estrogen only, missing).

Supplementary Table 3. Examination of confounding of physical activity-endometrial cancer risk with increased adjustment for covariates.

	Long-term LTPA pattern[a], OR (95% CI)				
Effect	Inactive (n=4 148)	Maintain low (n=12 577)	Maintain high (n=19 935)	Increasers (n=10 637)	Decreasers (n=14 059)
Endometrial cancers, No. (%)	149 (2.7)	245 (2.2)	439 (2.0)	259 (1.9)	376 (2.4)
Model 1: LTPA trajectory	Referent	0.81 (0.66, 0.99)	0.74 (0.61, 0.89)	0.70 (0.57, 0.85)	0.90 (0.74, 1.08)
Model 2: Model 1 + demographics[b]	Referent	0.81 (0.66, 1.00)	0.73 (0.61, 0.88)	0.70 (0.57, 0.85)	0.90 (0.75, 1.09)
Model 3: Model 2 + smoking + diet + calories	Referent	0.82 (0.67, 1.01)	0.76 (0.63, 0.91)	0.71 (0.58, 0.87)	0.93 (0.77, 1.13)
Model 4: Model 3 + oral contraceptives + MHT + parity	Referent	0.84 (0.69, 1.03)	0.79 (0.66, 0.96)	0.73 (0.60, 0.90)	0.97 (0.80, 1.18)
Model 5: Model 4 + BMI at 18y	Referent	0.85 (0.69, 1.04)	0.81 (0.67, 0.98)	0.74 (0.61, 0.91)	0.98 (0.81, 1.19)

[a] Participants with little or no physical activity (<1 hr/wk) at each age period were classified as Inactive; those maintaining low levels of activity over time were classified as Maintaining low activity; those maintaining high levels of activity over time were classified as Maintaining high activity; those that increased their activity over time were classified as Increasers; and those that decreased their activity over time were classified as Decreasers. CI = confidence interval; LTPA = leisure time physical activity ; MHT = menopausal hormone therapy use; OR = odds ratio.

[b] Includes age at baseline, race-ethnicity, and education

Supplementary Table 4. Risk for BMI classification at midlife (50-71 years) by long-term leisure time physical activity (LTPA) pattern.

	Long-term LTPA pattern[a], OR (95% CI)[b]				
BMI classification (kg/m^2)	Inactive (n=5,561)	Maintain low (n=11,125)	Maintain high (n=21,843)	Increasers (n=13,469)	Decreasers (n=15,707)
Overweight (25.0-29.9)	Referent	1.06 (0.98, 1.15)	0.84 (0.78, 0.90)	0.75 (0.70, 0.81)	1.29 (1.20, 1.39)
Obese - class I/II (30.0-39.0)	Referent	0.90 (0.83, 0.99)	0.50 (0.46, 0.55)	0.45 (0.41, 0.49)	1.33 (1.22, 1.45)
Obese - class III (≥40.0)	Referent	0.63 (0.51, 0.77)	0.32 (0.26, 0.39)	0.23 (0.19, 0.29)	1.47 (1.23, 1.76)

[a] Participants with little or no physical activity (<1 hr/wk) at each age period were classified as Inactive; those maintaining low levels of activity over time were classified as Maintaining low activity; those maintaining high levels of activity over time were classified as Maintaining high activity; those that increased their activity over time were classified as Increasers; and those that decreased their activity over time were classified as Decreasers. BMI = body mass index; LTPA = leisure time physical activity; CI = confidence interval

[b]Odds ratios were adjusted for: age (years), race-ethnicity (Non-Hispanic white, Non-Hispanic black, Hispanic, Other or missing), education (less than high school, high school, post high-school or some college, Bachelor degree or more, missing), smoking status/dose (never smoker, former smoker and ≤20 cigarettes/day, former smoker and >20 cigarettes/day, current smoker and ≤20 cigarettes/day, current smoker and > 20 cigarettes/day, missing), diet quality (2015 Healthy Eating Index; 0–100 points), total energy intake (kcal/day), alcohol consumption (grams/day), parity (number of births), use of oral contraceptives (never or <1 year, 1–4 years, 5–9 years, ≥10 years, missing), menopausal hormone therapy use (never, continuous estrogen plus progestin (EPT) use [15+ days progestin/month], sequential EPT [<15 days progestin/month], estrogen only, missing) and, body mass index at age 18 years (normal weight [<25.0 kg/m^2], overweight [25.0–29.9 kg/m^2], obese class I [30.0–34.9 kg/m^2], obese class II [35.0–39.9 kg/m^2], and obese class III [≥40.0 kg/m^2]).

Supplementary Table 5. Summary of mediation analysis without adjustments for BMI at age 18 yrs.

	Long-term LTPA patterns[a], HR (95% CI)				
Effect	Inactive (n=5,561)	Maintain low (n=11,125)	Maintain high (n=21,843)	Increasers (n=13,469)	Decreasers (n=15,707)
Total effect[b,c]	Referent	0.84 (0.66, 0.99)	0.79 (0.66, 0.95)	0.73 (0.59, 0.89)	0.98 (0.83, 1.21)
Indirect effect (though midlife BMI)[c]	Referent	0.95 (0.92, 0.99)	0.84 (0.82, 0.88)	0.84 (0.80, 0.87)	1.04 (1.01, 1.07)
Direct Effect[c]	Referent	0.88 (0.69, 1.04)	0.90 (0.78, 1.12)	0.88 (0.73, 1.06)	0.93 (0.80, 1.16)
Proportion of LTPA through BMI at midlife, % (95% CI)	Referent	29.4 (0.0, 100.0)	69.3 (39.5, 100.0)	57.5 (33.1, 100.0)	NE

[a] Participants with little or no physical activity (<1 hr/wk) at each age period were classified as Inactive; those maintaining low levels of activity over time were classified as Maintaining low activity; those maintaining high levels of activity over time were classified as Maintaining high activity; those that increased their activity over time were classified as Increasers; and those that decreased their activity over time were classified as Decreasers. [BMI – Body mass index; HR – hazard ratio; 95% CI – 95% confidence intervals; REF – reference; NE – Not estimated (i.e., the denominator for the proportion was approximately 0 and the estimation was not stable).

[b] The total effect presented in this table can differ from the effects provided in Supplementary Table 3 (model 4) by a residual amount.

[c] Hazard ratios were adjusted for: age (years), race-ethnicity (Non-Hispanic white, Non-Hispanic black, Hispanic, Other or missing), education (less than high school, high school, post high-school or some college, Bachelor degree or more, missing), smoking status/dose (never smoker, former smoker and ≤20 cigarettes/day, former smoker and >20 cigarettes/day, current smoker and ≤20 cigarettes/day, current smoker and > 20 cigarettes/day, missing), diet quality (2015 Healthy Eating Index; 0–100 points), total energy intake (kcal/day), alcohol consumption (grams/day), parity (number of births), use of oral contraceptives (never or <1 year, 1–4 years, 5–9 years, ≥10 years, missing), and menopausal hormone therapy use (never, continuous estrogen plus progestin (EPT) use [15+ days progestin/month], sequential EPT [<15 days progestin/month], estrogen only, missing). Models also included BMI in midlife (normal weight [<25.0 kg/m^2], overweight [25.0–29.9 kg/m^2], obese class I [30.0–34.9 kg/m^2], obese class II [35.0–39.9 kg/m^2], and obese class III [≥40.0 kg/m^2]) as a mediator of the activity-endometrial cancer association.

Supplementary Table 6. Total effect for selected long-term leisure time physical activity (LTPA) patterns stratified by confounders and BMI in midlife.

Stratified factor	Events No. (%)	Inactive[a] HR (95% CI)[c]	Maintain high[b] HR (95% CI)[c]	$P_{interaction}$
Age group				
50-59 (n=24,248)	504 (2.0)	1.00 (Ref)	0.72 (0.53, 0.99)	0.76
60-72 (n=43,457)	964 (2.2)	1.00 (Ref)	0.85 (0.67, 1.08)	
BMI at 18y, kg/m^2				
<25.0 (n=56,037)	1,182 (2.1)	1.00 (Ref)	0.80 (0.64, 0.99)	0.81
25.0+ (n=4,384)	149 (3.3)	1.00 (Ref)	0.83 (0.48, 1.44)	
BMI at midlife, kg/m2				
<25.0 (n=32,401)	452 (1.4)	1.00 (Ref)	1.13 (0.76, 1.69)	0.43
25.0+ (n=35,304)	1,016 (2.9)	1.00 (Ref)	0.78 (0.63, 0.97)	
Alcohol, g/day				
<1.1 (n=33,647)	804 (2.4)	1.00 (Ref)	0.78 (0.61, 0.99)	0.77
1.1+ (n=34,058)	664 (1.9)	1.00 (Ref)	0.90 (0.65, 1.23)	
2015 HEI, %[d]				
<70.2 (n=33,837)	731 (2.2)	1.00 (Ref)	0.77 (0.60, 0.99)	0.81
70.2+ (n=33,868)	737 (2.2)	1.00 (Ref)	0.86 (0.64, 1.15)	
Calories, kcal/d[e]				
<1.5 (n=33,846)	731 (2.2)	1.00 (Ref)	1.00 (0.75, 1.32)	0.02
1.5+ (n=33,859)	737 (2.2)	1.00 (Ref)	0.66 (0.51, 0.86)	
Parity, No.				
0 (n=12,103)	342 (2.8)	1.00 (Ref)	0.76 (0.54, 1.06)	0.08
1+ (n=55,602)	1,126 (2.0)	1.00 (Ref)	0.85 (0.68, 1.08)	
Ever used oral contraceptives				
Yes (n=27,788)	505 (1.8)	1.00 (Ref)	0.89 (0.62, 1.26)	0.57
No (n=39,533)	956 (2.4)	1.00 (Ref)	0.77 (0.61, 0.96)	
Menopause HT				
Continuous EPT (n=14,820)	228 (1.5)	1.00 (Ref)	0.85 (0.51, 1.44)	0.60

Sequential EPT + ET (n=14,002)	361 (2.6)	1.00 (Ref)	0.69 (0.47, 1.00)	
Never (n=34,634)	781 (2.3)	1.00 (Ref)	0.84 (0.65, 1.09)	
Diabetes				
Yes (n=3,982)	125 (3.1)	1.00 (Ref)	0.57 (0.32, 1.03)	0.63
No (n=63,723)	1,343 (2.1)	1.00 (Ref)	0.86 (0.70, 1.05)	
Cardiovascular disease				
Yes (n=4,578)	100 (2.2)	1.00 (Ref)	0.82 (0.40, 1.68)	0.51
No (n=63,127)	1,368 (2.2)	1.00 (Ref)	0.81 (0.67, 0.99)	

[a]Reported no activity at each age period (n=5,561); Abbreviations: HT = hormone therapy; EPT = Estrogen-plus-progestin therapy; ET = Estrogen therapy; HEI = Healthy Eating Index;BMI = body mass index; HR = hazard ratio; CI = confidence interval

[b]Maintained high levels of activity over time (n=21,843);

[c]Hazard ratios were adjusted for: age (years), race-ethnicity (Non-Hispanic white, Non-Hispanic black, Hispanic, Other or missing), education (less than high school, high school, post high-school or some college, Bachelor degree or more, missing), smoking status/dose (never smoker, former smoker and ≤20 cigarettes/day, former smoker and >20 cigarettes/day, current smoker and ≤20 cigarettes/day, current smoker and > 20 cigarettes/day, missing), diet quality (2015 Healthy Eating Index; 0–100 points), total energy intake (kcal/day), alcohol consumption (grams/day), parity (number of births), use of oral contraceptives (never or <1 year, 1–4 years, 5–9 years, ≥10 years, missing), menopausal hormone therapy use (never, continuous estrogen plus progestin (EPT) use [15+ days progestin/month], sequential EPT [<15 days progestin/month], estrogen only, missing) and, body mass index at age 18 years (normal weight [<25.0 kg/m^2], overweight [25.0–29.9 kg/m^2], obese class I [30.0–34.9 kg/m^2], obese class II [35.0–39.9 kg/m^2], and obese class III [≥40.0 kg/m^2]), while excluding the confounder of interest.

[d]2015 HEI scores range from 0 (least healthy) to a 100 (most healthy) and describe diet quality as recommended by the 2015-2020 Dietary Guidelines for Americans.

[e]Indicates kcal/day per 1000.

Supplementary Table 7. Total effect for Maintaining high physical activity vs. Inactive (referent) by time of follow-up and excluding women that lost weight in the previous 10 years to baseline.

Restriction factor	Events	Inactive[a] HR (95% CI)[c]	Maintain high[b] HR (95% CI)[c]
Follow-up			
2+ (n=64,562)	1,251	1.00 (Ref)	0.74 (0.60, 0.90)
4+ (n=61,510)	1,030	1.00 (Ref)	0.72 (0.58, 0.90)
6+ (n=58,226)	815	1.00 (Ref)	0.75 (0.58, 0.95)
Excluding weight loss (n=65,500)[d]	1,430	1.00 (Ref)	0.80 (0.66, 0.97)

[a]Reported no activity at each age period (<1 hr/wk; n=5,561). HR = hazard ratio; CI = confidence interval. HR = hazard ratio; CI – confidence interval

[b]Maintained high levels of activity over time (n=21,843);

[c]Hazard ratios were adjusted for: age (years), race-ethnicity (Non-Hispanic white, Non-Hispanic black, Hispanic, Other or missing), education (less than high school, high school, post high-school or some college, Bachelor degree or more, missing), smoking status/dose (never smoker, former smoker and ≤20 cigarettes/day, former smoker and >20 cigarettes/day, current smoker and ≤20 cigarettes/day, current smoker and > 20 cigarettes/day, missing), diet quality (2015 Healthy Eating Index; 0–100 points), total energy intake (kcal/day), alcohol consumption (grams/day), parity (number of births), use of oral contraceptives (never or <1 year, 1–4 years, 5–9 years, ≥10 years, missing), menopausal hormone therapy use (never, continuous estrogen plus progestin (EPT) use [15+ days progestin/month], sequential EPT [<15 days progestin/month], estrogen only, missing) and, body mass index at age 18 years (normal weight [<25.0 kg/m^2], overweight [25.0–29.9 kg/m^2], obese class I [30.0–34.9 kg/m^2], obese class II [35.0–39.9 kg/m^2], and obese class III [≥40.0 kg/m^2]).

[d]Excluding women that lost weight recently, i.e., those that reported a lower BMI at baseline when compared to the previous 1-10 years.

Supplementary Figure

Supplementary Figure 1. AARP Risk Factor Questionnaire item used to assess long-term participation in leisure-time physical activity.

55. Read the list of examples of moderate and vigorous activities in the box below.

EXAMPLES OF MODERATE AND VIGOROUS ACTIVITIES:

Tennis	Heavy gardening	Cheerleading/drill team	Rowing
Golf (walking)	Weight lifting	Handball/racquetball	Aerobics
Biking	Basketball/baseball	Hiking/climbing mountains	Jogging/running
Swimming	Football/soccer	Fast walking/fast dancing	Heavy housework

Think back to the ages and times listed in the table below. Mark the circles that best describe how often you participated in moderate and vigorous activities at the ages and time listed. DO NOT INCLUDE ACTIVITIES THAT YOU REPORTED IN QUESTIONS 48 - 51 ON PAGE 13.

How often did you participate in moderate and vigorous activities at the following ages and time?	HOW OFTEN (MARK ONLY ONE RESPONSE)					
	Never	Rarely	Weekly, but less than 1 hour per week	1-3 hours per week	4-7 hours per week	More than 7 hours per week
15-18 years old	○	○	○	○	○	○
19-29 years old	○	○	○	○	○	○
35-39 years old	○	○	○	○	○	○
in the past 10 years	○	○	○	○	○	○