



Physical activity and risk of endometrial cancer in the Norwegian Women and Cancer (NOWAC) Study

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Manuscripts

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3 1 **Physical activity and risk of endometrial cancer in the Norwegian Women**
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5 2 **and Cancer (NOWAC) Study**

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16
17 7 **Running title: Physical activity and endometrial cancer**

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24 10 **Keywords:** Endometrial cancer; physical activity; prospective study; population attributable
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26 11 fraction.

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31 13 **Novelty and impact statements:**

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33 14 We found evidence of a dose-response association between physical activity and overall
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35 15 endometrial cancer. The novelty include use of repeated measurements for physical activity
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37 16 and confounders combined with multiple imputation to address attrition, which is a particular
38
39 17 problem in observational epidemiology. As a nationally representative cohort our study gave
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41 18 us an unique opportunity to calculate robust population attributable fractions. 22% of
42
43 19 endometrial cancer could be avoided if women increase their physical activity level.

44 20 **Abbreviations:**

45 21 BMI – body mass index
46 22 CI – confidence interval
47 23 CUP - Continous Update Project
48 24 PA – physical activity
49 25 PAF – population attributable fractions
50 26 HR – hazard ratio
51 27 RR – relative risk
52 28 NOWAC – The Norwegian Women and Cancer Study
53 29 WCRF/AICR - World Cancer Research Fund/American Institute for Cancer Research
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19

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26 **Author's contributions**

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28 KBB, EW and IL designed the study. IL and KBB performed all statistical analyses, and
29
30 drafted the manuscript. EW, MJ, and OG critically revised the manuscript. TB participated in
31
32 the statistical analyses and revised the manuscript critically. All authors read and approved the
33
34 final manuscript.
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3 52 **Abstract**
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5 53 Few studies have investigated the association between endometrial cancer and physical
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7 54 activity (PA) using repeated measures of PA and different subtypes of endometrial cancer.
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10 55 We aimed to investigate the association between endometrial cancer and PA level at two
11
12 56 points in time in women with different body mass index (BMI) profiles, and to calculate the
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14 57 population attributable fraction (PAF) of endometrial cancer for low PA levels.
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16 58 We included 82,759 women with complete information on PA at baseline in the Norwegian
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18 59 Women and Cancer Study; 52,370 had follow-up information on PA. 687 endometrial cancer
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20 60 cases were identified. Multivariate cox proportional hazard models were used to estimate
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22 61 hazard ratios (HR) and 95% confidence intervals (CI). The PAF indicated the proportion of
23
24 62 endometrial cancer that could be avoided in the population if these women had a higher PA
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26 63 level.
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29 64 There was a statistically significant association between low PA levels at baseline and follow-
30
31 65 up and endometrial cancer risk, with a dose-response trend (lowest PA level: HR=1.60, 95%
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33 66 CI 1.16-2.20; highest PA level: HR=0.73, 95% CI 0.45-1.16 compared to the median).
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36 67 Analyses that included follow-up measurements yielded similar results. 21.9% (95% CI 7.1-
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38 68 34.3) of endometrial cancers could be avoided if women with low PA levels (≤ 4 in a 1-10
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40 69 degree self reported PA scale) increased their PA levels to 5-10.
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43 70 We found an inverse dose-response association between PA and endometrial cancer,
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45 71 independent of BMI. In this nationally representative cohort, 21.9% of endometrial cancers
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47 72 could potentially be avoided if PA levels increased to higher PA levels.
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74 **Introduction**

75 Endometrial cancer is the sixth most common cancer, and the most frequent gynecologic
76 malignancy among women in Norway. In 2014, 727 new cases were diagnosed and 81
77 women died of the disease [1]. Established risk factors for endometrial cancer include use of
78 exogenous estrogens unopposed by progestagens, early menarche (10-12 years of age), late
79 menopause, nulliparity, diabetes mellitus, and obesity. Currently, the majority of endometrial
80 cancer, and about half of the cases in postmenopausal women are attributable to being
81 overweight or obese [2-4]. As the population ages and the prevalence of overweight, obesity,
82 and sedentary lifestyle increase, the incidence of endometrial cancer is also expected to
83 increase, especially in postmenopausal women [5, 6]. Thus primary prevention of endometrial
84 cancer through modifiable lifestyle factors is of potential public health importance.

85 Physical activity (PA) is a modifiable lifestyle factor, which is important in the regulation
86 of hormones and metabolic pathways. It is also associated with weight control, and thus may
87 reduce endometrial cancer risk [7-9]. A pooled analysis of nine cohorts from Europe and the
88 United States included 1.44 million participants and found a 21% reduced risk of endometrial
89 cancer associated with recreational PA [10]. However, within individual studies, results are
90 inconsistent [8]. For example, the Women's Health Study did not find any relationship
91 between recreational PA and walking and endometrial cancer risk [11]. Similarly, there was
92 no significant association between total PA – including occupational, recreational, and
93 household-related PA – and endometrial cancer risk in the European Prospective Investigation
94 into Nutrition and Cancer [12]. The 2007 evaluation by the World Cancer Research
95 Fund/American Institute for Cancer Research (WCRF/AICR) concluded that there is a
96 probable relationship between PA and endometrial cancer despite the variety of PA
97 assessments not allowing for meta-analysis on dose-response [7]. This conclusion was
98 supported in their Continuous Update Project (CUP) report from 2013 [8]. Of four cohort

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3 99 studies published after the 2013 CUP report [10, 13-15], three found an inverse association
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5 100 between recreational PA and endometrial cancer risk [10, 15, 14], and one did not [13].
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7 101 Few studies have investigated the association between endometrial cancer and PA using a
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9 102 total and repeated measure of PA and different subtypes of endometrial cancer [12, 16, 17].
10
11 103 Endometrial cancer is classified as type I (estrogen dependent), which constitutes the majority
12
13 104 of cases (about 80%), and type II (estrogen independent), based on clinical, endocrine, and
14
15 105 epidemiological observations. The most common histological subtypes of endometrial cancer
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17 106 are endometrioid carcinoma, serous carcinoma, carcinosarcoma, and clear cell carcinoma
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19 107 [18]. While the association between body mass index (BMI) and endometrial cancer is well
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21 108 established, the relationship between PA and endometrial cancer in women with different
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23 109 body sizes remains unclear.
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27 110 The present study aimed to investigate the association between endometrial cancer and PA
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29 111 level at two points in time in women with different BMI profiles in the Norwegian Women
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31 112 and Cancer (NOWAC) Study, and to calculate the population attributable fraction (PAF) of
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33 113 endometrial cancer for low PA levels.
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3 116 **Methods**

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5 117 **The NOWAC Study**

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7 118 The NOWAC Study is a nationally representative cohort study that has been described in
8
9 119 detail previously [19, 20]. Briefly, random samples of Norwegian women aged 30-70 years
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11 120 were invited to participate during three waves of data collection (1991/92, 1996/97, and
12
13 121 2003/04) [20]. More than 172,000 women completed a questionnaire with detailed questions
14
15 122 regarding lifestyle, diet, and health, and were enrolled in the study (overall response rate:
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17 123 52.7%). The NOWAC Study was approved by the Regional Committee for Medical Research
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19 124 Ethics and the Norwegian Data Inspectorate, and all participants included in the study gave
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21 125 written informed consent.
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25 126 In this analysis we used information from enrollment questionnaires completed in the
26
27 127 period from 1996 to 2004 (baseline), and those with follow-up questionnaires completed 6-8
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29 128 years after enrollment. In total 101,321 women completed questionnaires in these periods and
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31 129 were eligible for inclusion in this study. We excluded women with prevalent cancers other
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33 130 than non-melanoma skin cancer at baseline (n=4,454), those who emigrated or died before the
34
35 131 start of follow-up (n=20), those with hysterectomy (n=5,426), and those who had missing
36
37 132 information on PA level at baseline (n=8,662). Thus, the final analytical study sample
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39 133 consisted of 82,759 women. Follow-up information on PA level, smoking, weight, and height
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41 134 was available for for 52,370 (63.3%) of these women.
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47 136 **Assessment of PA level and covariates**

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49 137 PA level was assessed in the NOWAC questionnaires on a 10-point scale by the following
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51 138 question: *“By physical activity we mean activity both at work and outside work, at home, as
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53 139 well as training/exercise and other physical activity, such as walking, etc. Please mark the
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55 140 number that best describes your level of physical activity; 1 being very low and 10 being very
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3 141 *high*". This PA scale has been validated [21] and refers to the total amount of PA across
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5 142 different domains, including recreation, occupation, transportation, and household in one
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7 143 global score. Moderate, but significant Spearman's rank correlation coefficients were found
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9 144 (range: 0.36-0.46; $P < 0.001$) between PA level at enrollment and concurrent outcomes from
10
11 145 criterion measures of a combined sensor monitoring heart rate and movement. The PA scale
12
13 146 appeared valid to rank PA level in Norwegian women, but not to quantify a definite dose of
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15 147 PA [21].

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18 148 Information on the covariates height, weight, age at menarche, parity, oral contraceptive
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20 149 use, menopausal status, age at menopause, hormone therapy use, years of education, smoking
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22 150 status and alcohol consumption, were obtained from NOWAC questionnaires. The women
23
24 151 were considered postmenopausal if they stated that the period had stopped or reported use of
25
26 152 hormonal therapy if they were ≥ 53 years. This cut-off point is based on the definition used in
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28 153 the the Million Women Study [22], and has been used by the NOWAC study earlier [23].
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30 154 Information on height and weight was used to calculate BMI (kg/m^2).
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35 36 156 **Cancer incidence, death, and emigration**

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38 157 Women diagnosed with a primary, invasive, malignant neoplasm of the endometrium
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40 158 (International Statistical Classification of Diseases, Injuries and Causes of Death Revision 7
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42 159 codes 172.0 [24]) were identified through linkage to the Cancer Registry of Norway, from
43
44 160 which date of diagnosis and morphology (International Classification of Diseases for
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46 161 Oncology, 3rd edition) were also obtained. Based on the morphology, endometrial cancers
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48 162 were categorized into overall endometrial cancer (all subtypes), endometrioid carcinoma, type
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50 163 1 endometrial cancer (adenocarcinoma NOS, endometrioid, and squamous carcinomas), and
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52 164 other subtypes (non-endometrioid or non-type 1).
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3 165 Information on date of death or emigration was obtained through linkage to the
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5 166 Norwegian National Population Register.

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10 168 **Statistical methods**

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12 169 Analyses using baseline data only

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14 170 We used Cox proportional hazard regression models to calculate hazard ratios (HRs) with
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16 171 95% confidence intervals (CIs) comparing five categories of PA level (1-2, 3-4, 5-6, 7-8, and
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18 172 9-10). PA level 5-6 was set as the reference group. Follow-up time was defined as the interval
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20 173 between age at baseline and age at cancer diagnosis, death, emigration, or the end of follow-
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22 174 up (31 December 2013), whichever came first.

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24 175 Departures from the proportional hazards assumption in the Cox models were tested through
25
26 176 the inclusion of an interaction variable between categories of PA and underlying time (age). A
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28 177 preliminary analysis of baseline data only was used to select the covariates that were adjusted
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30 178 for in the final models. In the preliminary model, we adjusted for: height (in metres), BMI
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32 179 (normal weight: <25, overweight: 25–29.9, obese: ≥ 30 kg/m²), age at menarche (<12, 13-14,
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34 180 15+ years), parity (0, 1, 2, 3, 4+) , oral contraceptive use (ever/never), menopausal status
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36 181 (premenopausal, perimenopausal, postmenopausal, hormone therapy use ≥ 53 years), hormone
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38 182 therapy use (ever/never), years of education (≤ 9 , >9-12, ≥ 13 years), smoking status (never,
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40 183 former, current), alcohol consumption (grams per day), and diabetes mellitus (yes/no). The
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42 184 removal of each covariate had to be associated with a change in the regression coefficients of
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44 185 at least 10% in any of the categories of PA level to be included in the final model. To test for
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46 186 linear trend, we used the original, 10-point PA scale, modelled as a continuous variable in the
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48 187 analyses. Interactions (log likelihood test) between PA and the above-mentioned categories of
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50 188 BMI, educational attainment and smoking status were tested. The Wald χ^2 statistic was used
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52 189 to test for heterogeneity between normal weight and obese women.
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192 Analyses using repeated PA measurements

193 We used the method proposed by Hu et al [25], i.e., baseline data was used until follow-up
194 information became available, death, or emigration, whichever occurred first. Thereafter
195 follow-up information was applied until death, emigration, or the end of the study period,
196 which ever occurred first. In the analysis using repeated PA measurements, we also used
197 follow-up information on BMI and smoking once it became available.

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199 Complementary analysis - multiple imputation

200 Compared to women who did not drop out of the study, those who dropped out of the study at
201 follow-up (n=30,389 (36.7%)), were more often overweight (31.4% vs 29.2%) or obese
202 (10.3% vs 8.6%), more often reported oral contraceptive use (46.6% vs 43.5%) and hormone
203 therapy use (36.7% vs 31.7%), more often had a history of diabetes mellitus (2.9% vs 1.7%),
204 and had fewer years of education (24.3% vs 23.7%). They were also more often current
205 smokers, but on average they had a similar PA level and alcohol consumption as women who
206 did not drop out of the study. In order to deal with dropouts, we used multiple imputation
207 models [26] and compared the results with those of complete-case analyses. Multiple
208 imputation models were used under the assumption that data was missing at random. To
209 reduce sampling variability, we created 20 replicate datasets from the imputation simulation
210 [27]. We used the outcomes overall endometrial cancer, type 1 endometrial cancer, and
211 endometrioid carcinoma. Nelson-Aalen cumulative hazard estimator was included as a
212 predictor in the imputation models [28]. The estimates from the 20 imputed datasets were
213 combined using Rubin's rules [29]. All the analyses and multiple imputations were done in
214 STATA version 14.0 (Stata Corp, College Station, TX, USA).

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5 216 PAF calculation6
7 217 We calculated the PAF to estimate the proportion of endometrial cancer that could be avoided8
9 218 in the population if women had different PA levels, using the formula: $PAF = Pe * (RRe -$ 10
11 219 $1) / [Pe * RR + (1 - Pe)]$, where Pe is the proportion of PA level in the study population and RRe is12
13 220 the RR in the model adjusting for BMI (model 1) and the final baseline multivariable14
15 221 proportional hazards regression model (model 2), including all aforementioned confounders16
17 222 and BMI. We calculated two-sided 95% CIs for the PAFs using the PUNAF Stata module18
19 223 [30]. The PA levels were divided into two levels; levels 1 to 4 were classified as exposed to20
21 224 low PA levels and levels 5-10 as unexposed to low PA levels. The PAF was interpreted as the22
23 225 proportion of overall endometrial cancers that would not occur in the average population if24
25 226 PA levels were between 5 and 10 according to the scale.26
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Results

The median age at baseline was 51 years. During a mean follow-up time of nearly 13 years, 687 cases of endometrial cancer were identified, with type 1 endometrial cancer (adenocarcinoma not otherwise specified [NOS], endometrioid and squamous carcinoma) accounting for 83.8% of the cases. The age at diagnosis ranged between 42 and 86 years, with a mean of 62 years of age. Nearly half (43%) of the women reported a PA level between 5 and 6 (Table 1), and approximately 74% of the women reported a PA level between 5 and 10. Women with a PA level >5 had a lower BMI, used less hormone therapy, reported less diabetes mellitus, and were more often never smokers compared to women reporting low PA levels.

Multivariable models of the associations between baseline and one follow-up measurement of PA and endometrial cancer risk shows that compared to women with a PA level of 5-6, those with a PA level of 1-2 had a 60% higher risk of overall endometrial cancer (HR=1.60, 95% CI 1.16-2.20). For analyses using repeated PA measurements, the corresponding risks adjusted for BMI and smoking status were similar to those obtained when using baseline data only (HR=1.54, 95% CI 1.01-2.). In analyses using baseline data only and those using repeated PA measurements, BMI and smoking status were negatively associated with the risk of type 1 endometrial cancer and endometrioid carcinomas. Compared to the age-adjusted models, the associations were attenuated in the multivariable adjusted models that included BMI (Table 2).

Interactions between PA and categories of BMI, educational attainment and smoking status were not significant. However, as BMI is a strong risk factor for endometrial cancer, we decided to investigate the association between PA and endometrial cancer risk in normal weight, overweight, and obese women, even though the interaction term was not significant (p=0.49). When analyses were stratified by BMI category the PA levels 7-10 were collapsed,

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3 254 PA was not associated with overall endometrial cancer among normal-weight women in
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5 255 analyses using baseline data only ($HR_{PA(1-2) \text{ vs } (5-6)}=1.32$, 95% CI 0.71-2.45). The
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7 256 corresponding association in obese participants was $HR_{PA(1-2) \text{ vs } (5-6)}=3.08$ (95% CI 1.76-5.39)
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9 257 ($p_{\text{heterogeneity}}=0.05$) (Table 3).

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11 Using multiple imputation, we found that the estimates at all levels of adjustment and for
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13 259 all endpoints (overall endometrial cancer, type 1 endometrial cancer, and endometrioid
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15 260 carcinoma) were consistent with those obtained from the complete-case analyses (Table 4).
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17 261 PAF calculations showed that if women with a PA level ≤ 4 increased to levels 5-10 in the
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19 262 scale, 21.9% (95% CI: 7.1-34.3) of endometrial cancers could be avoided (Table 5). PAF
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21 263 calculations based on the proportional hazards regression model including BMI yielded a
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23 264 lower proportion (17%, 95% CI: 2.3-29.5) (Table 5). The results did not differ substantially
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25 265 for subtypes of endometrial cancer (Supplemental table 1)
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31 267 **Discussion**

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33 268 In this large Norwegian cohort we found an inverse dose-response association between PA
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35 269 and endometrial cancer overall, type 1 endometrial cancer, and endometrioid carcinoma. The
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37 270 results were consistent when using baseline data on PA and when using repeated PA
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39 271 measurements, as well as when multiple imputation was used. Our findings further suggest
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41 272 that the association between PA and endometrial cancer is independent of BMI, as risk
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43 273 estimates were attenuated, but still significant, when BMI was incorporated in the statistical
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45 274 models. Stratification by BMI category indicated that the risk of low PA on endometrial
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47 275 cancer was statistically significant among obese women only (although the test for interaction
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49 276 was not statistically significant, $p=0.49$). Among women with PA levels ≤ 4 , 21.9% of
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51 277 endometrial cancer could potentially be avoided if these women adopted a PA level between
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53 278 5-10 in the scale.
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3 279 Other cohort studies investigating the association between total PA levels – which include
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5 280 domains such as recreation, occupation, transportation, and household – and endometrial
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7 281 cancer are sparse; most studies measured recreational PA only and few studies use repeated
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9 282 measurements of PA. In contrast to our results, the European Prospective Investigation into
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11 283 nutrition and Cancer reported a non-significant trend (p-trend 0.36) for total PA (including the
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13 284 domains recreation, occupation, and household) when comparing active with inactive women
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15 285 (multivariable adjusted model including BMI: HR=0.88, 95% CI 0.61-1.27) [12]. This was
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17 286 similar for the Breast Cancer Detection Demonstration Project study, which measured the
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19 287 total intensity of PA and found no significant associations with endometrial cancer [31].
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21 288 Findings from the Netherlands Cohort Study on Diet and Cancer showed that total baseline
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23 289 non-occupational PA was inversely associated with endometrial cancer, with a lower risk
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25 290 observed for a PA corresponding to >30 minutes per day [17, 32]. In a Swedish cohort the
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27 291 risk was decreased, although this decrease was not significant [16].
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32 Several studies have reported on recreational PA and endometrial cancer. Nine
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34 293 prospective cohort studies on recreational PA were included in the WCRF/AICR CUP report
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36 294 up to 2012 [8], but due to different measures of PA, the meta-analysis of these studies only
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38 295 looked at the highest vs lowest PA level (RR=0.73, 95% CI 0.58-0.93), and these results were
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40 296 attenuated when the model was adjusted for BMI (RR=0.80, 95% CI 0.69-0.92). A limitation
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42 297 of this meta-analysis was the high heterogeneity ($I^2=75.9%$) of the individual studies [8].
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44 298 Indeed, only three of these studies [33, 32, 34] found significant inverse associations, three
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46 299 found no significant association [35, 11, 36], and three [37, 12, 16] found an inverse, but
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48 300 insignificant association between endometrial cancer and recreational PA. Since the
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50 301 publication of the WCRF/AICR CUP report from 2012 we have identified four additional
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52 302 prospective cohort studies on recreational PA and endometrial cancer [10, 13-15]. The
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54 303 Nurses' Health study investigated recreational PA in the past year and found no association
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3 304 between baseline recreational PA and endometrial cancer risk, however, brisk walking time
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5 305 ≥ 3 hours per week was inversely associated with endometrial cancer [15]. In the California
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7 306 Teachers Study cohort, moderate and vigorous recreational PA was associated with a 25%
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9 307 lower endometrial cancer risk [13]. The findings of Land et al [14] are in accordance with our
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11 308 findings, although they studied recreational PA and had a small number of cases in a
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13 309 population of women at high risk for breast cancer. A large pooled analysis of 12 cohorts was
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15 310 recently published and reported a HR of 0.79 (95% CI 0.68-0.92) in the association between
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17 311 recreational PA and endometrial cancer based on 5346 cases. However, the degree of
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19 312 heterogeneity between cohorts was high ($I^2=69\%$)[10].

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23 313 Analysis of occupational PA measured twice during 1974 and 1981 in a Norwegian study
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25 314 showed a significant trend, with a reduced risk for women who were consistently moderately
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27 315 active; however, the association was attenuated in the multivariable model and the trend was
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29 316 no longer significant [36]. The WCRF/AICR CUP report [8] included four cohort studies [16,
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31 317 38, 12, 39], none of which found a significant association between occupational PA and
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33 318 endometrial cancer. In a highest vs lowest occupational PA meta-analysis, the summary RR
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35 319 was 0.79 (95% CI 0.71-0.88), with a high degree of heterogeneity between studies ($I^2=$
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37 320 75.9%) and concluded a probable inverse association between occupational PA and
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39 321 endometrial cancer [8].

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43 322 Overweight and obesity are strong risk factors for endometrial cancer, and studies suggest
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45 323 that the association between PA and endometrial cancer is either mediated or confounded by
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47 324 body weight, which can affect hormone profiles. Therefore, it is important to model the
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49 325 association both with and without adjustment for BMI [15]. In our study, adjustment for BMI
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51 326 in the multivariable analyses attenuated the associations. However, a modest inverse
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53 327 association remained, suggesting that PA is independently associated with endometrial
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55 328 cancer. Simultaneously, the analyses of the different BMI categories showed that the
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3 329 association was more pronounced in obese than in normal-weight women. In our data, obesity
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5 330 may confound the association between PA and overall endometrial cancer. Our findings are in
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7 331 accordance with Friberg et al [16]. However, Moore et al adjusted for BMI in the association
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9 332 between recreational PA and endometrial cancer and showed an attenuation of the estimates
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11 333 from a significant towards a non-significant result compared to multivariable models
12
13 334 unadjusted for BMI (HR=0.98, 95% CI 0.89-1.09 vs HR=0.79, 95% CI 0.68-0.92) . This was
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15 335 similar to several previous studies [14, 15, 33, 37]. Some studies have found a statistically
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17 336 significant increased endometrial cancer risk in both inactive and active overweight women
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19 337 [11], which correspond to our findings. Others have shown an effect modification, where the
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21 338 inverse relationship was only seen among overweight or obese women [10, 37]. As in our
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23 339 study, several other studies have reported no significant effect modification for BMI [33, 12,
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25 340 16, 17, 31].

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29 341 Heterogeneity in different study results may be explained by variations in the methods
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31 342 used to assess PA (self-administered questionnaires, interviews, or use of job titles); PA
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33 343 domains (recreation, occupation, transportation, household); frequency, duration, and
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35 344 intensity of PA; and time periods in life when PA was measured, as well as different statistical
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37 345 methods used in the data analysis [40]. Nevertheless, there is substantial biological evidence
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39 346 to support a potential protective role of PA on endometrial cancer. The mechanisms involved
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41 347 have been hypothesized as affecting endogenous sex hormone levels, insulin-mediated
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43 348 pathways, and maintenance of energy balance [41].

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47 349 Physical inactivity is considered an important risk factor for different cancers [42-44]. The
48
49 350 consistent associations between low PA levels and endometrial cancer risk in our study
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51 351 justify the estimation of PAFs. Our definition of low PA levels was based on self-reported PA
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53 352 using a validated 10-point scale [21]. Our PAF estimation represents the minimum move
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55 353 required from low to higher levels of PA to create a significant change in the incidence of
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3 354 endometrial cancer (21.9%, 95% CI: 7.1-34.3). However, the definite dose cannot be
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5 355 quantified and our results must be interpreted with caution. In the UK, Parkin found a PAF for
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7 356 endometrial cancer of 3.8% attributable to exercising less than the minimum recommended
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9 357 amount [43]. The proportion related to inadequate PA in the UK in 2002 was 30% for
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11 358 endometrial cancer, however that compared the highest (≥ 60 minutes) and lowest (< 30
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13 359 minutes) PA levels, which gives a higher reference category than the recommendation of PA
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15 360 [45]. To quantify the PAF requires a realistic population distribution of the exposure of
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17 361 interest, which in our study is PA. We consider our cohort to be a nationally representative
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19 362 Norwegian cohort with a reliable population distribution of PA, and as such it should give a
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21 363 robust estimate. Furthermore, it is valuable to evaluate the impact of different factors in
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23 364 cancer prevention, which is helpful in prioritizing cancer prevention and intervention
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25 365 strategies.

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29 366 A major strength of our study is its prospective, population-based design, and the use of a
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31 367 high-quality, national cancer registry to identify endometrial cancer cases [20]. The large
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33 368 sample size and representativeness of the Norwegian female population 30 to 70 years of age
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35 369 gives a unique opportunity to calculate robust PAF estimates. The PA scale has been validated
36
37 370 [21] and correlated well with all-cause mortality rates [46]. Furthermore, PA level, BMI, and
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39 371 smoking were re-assessed at follow-up. Self-reported BMI has been validated for the
40
41 372 NOWAC study, indicating that there was a substantial agreement between self-reported and
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43 373 measured BMI values [47]. There was, however, a small but statistically significant under-
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45 374 reporting of weight, which would affect self-reported BMI; this tendency was largest among
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47 375 overweight and obese women [20, 47]. A survey of the PA levels in the adult population in
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49 376 Norway showed that 34% of women reached the national guidelines for PA [48]. This
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51 377 proportion is higher than in our study. The relatively large number of cases made it possible to
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53 378 investigate subtypes of endometrial cancer, however the proportion of type 2 endometrial
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3 379 cancer was too low to allow for separate analyses. Multiple imputation of missing data, in
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5 380 addition to complete-case analysis, confirmed our results. The PA assessment in our study
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7 381 comprised all areas of PA, not only recreational PA. However, the total self-reported measure
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9 382 of PA cannot differentiate intensity, duration, and frequency of PA, nor the type of PA in our
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11 383 study, and given the self report of PA, measurement errors cannot be ruled out. However,
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13 384 measurement errors would likely lead to a non-differential bias and a potential
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15 385 underestimation of the true effect. The PA assessment used in this study may not apply to
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17 386 women in other countries. Moreover, the potential for residual confounding, in particular by
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19 387 BMI, remains.
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389 **Conclusions**

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27 390 Overall, we found an inverse dose-response association between PA and endometrial cancer
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29 391 with similar findings for subtypes of endometrial cancer. This risk was higher in obese
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31 392 women. Also, 21.9% of the endometrial cancer cases could be attributable to low levels of
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33 393 PA, and could potentially be avoided if women attained a higher PA level.
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41 396 **Ethical approval:** All procedures performed in studies involving human participants were in
42
43 397 accordance with the ethical standards of the institutional and/or national research committee
44
45 398 and with the 1964 Helsinki declaration and its later amendments or comparable ethical
46
47 399 standards.
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45 541 HelseDirektoratet, Oslo2015.

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7 **1 Physical activity and risk of endometrial cancer in the Norwegian Women**
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9 **2 and Cancer (NOWAC) Study**

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11 3 Kristin B Borch^{1*}, Elisabete Weiderpass^{1,2,3,4}, Tonje Braaten¹, Mie Jareid¹, Oxana A
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13 4 Gavrilyuk¹, Ildir Licaj¹

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19 7 **Running title: Physical activity and endometrial cancer**

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21 8 **Word count:** Abstract: 250; main text: 3 853+9

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23 9 **Tables:** 35; (supplementary tables: 1-figures:-1)

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25 10 **Keywords:** Endometrial cancer; physical activity; prospective study; population attributable
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27 11 fraction.

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31 13 **Novelty and impact statements:**

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33 14 We found evidence of a dose-response association between physical activity and overall
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35 15 endometrial cancer. The novelty include use of repeated measurements for physical activity
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37 16 and confounders combined with multiple imputation to address attrition, which is a particular
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39 17 problem in observational epidemiology. As a nationally representative cohort our study gave
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41 18 us an unique opportunity to calculate robust population attributable fractions. 3422% of
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43 19 endometrial cancer could be avoided if women increase their physical activity to the
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45 20 ~~recommended~~ level.

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60 21 **Abbreviations:**

22 BMI – body mass index

23 CI – confidence interval

24 CUP - Continous Update Project

25 PA – physical activity

26 PAF – population attributable fractions

27 HR – hazard ratio

28 RR – relative risk

29 NOWAC – The Norwegian Women and Cancer Study

30 WCRF/AICR - World Cancer Research Fund/American Institute for Cancer Research

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16 41

17 42
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19 44

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22 47

23 48
24 49 **Conflict of interest:** The authors declare that they have no conflict of interest.
25 50
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27 52
28 53 **Author's contributions**
29 54

30 55 KBB, EW and IL designed the study. IL and KBB preformed all statistical analyses, and
31 56 drafted the manuscript. EW, MJ, and OG critically revised the manuscript. TB participated in
32 57 the statistical analyses and revised the manuscript critically. All authors read and approved the
33 58 final manuscript.
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Abstract

Few studies have investigated the association between endometrial cancer and physical activity (PA) using repeated measures of PA and different subtypes of endometrial cancer.

We aimed to investigate the association between endometrial cancer and PA level at two points in time in women with different body mass index (BMI) profiles, and to calculate the population attributable fraction (PAF) of endometrial cancer for low PA levels.

We included 82,759 women with complete information on PA at baseline in the Norwegian Women and Cancer Study; 52,370 had follow-up information on PA. 687 endometrial cancer cases were identified. Multivariate cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). The PAF indicated the proportion of endometrial cancer that could be avoided in the population if these women had a higher PA level, ~~corresponding to ≥ 150 minutes of moderate/vigorous PA per week.~~

There was a statistically significant association between low PA levels at baseline and follow-up and endometrial cancer risk, with a dose-response trend (lowest PA level: HR=1.~~8560~~, 95% CI 1.~~1636~~-2.~~2053~~; highest PA level: HR=0.7~~43~~, 95% CI 0.45-1.1~~26~~ compared to the median). ~~The Analyses that included including follow-up measurements yielded similar results. se associations were attenuated after adjustment for BMI, but remained significant.~~ 23.94% (95% CI 7.16-34.349) of endometrial cancers could be avoided if women with low PA levels (≤ 4 in a 1-10 degree self reported PA scale) increased their PA levels to 5-10 at least 150 minutes/week.

We found an inverse dose-response association between PA and endometrial cancer, independent of BMI. In this nationally representative cohort, 21.9% One of four endometrial cancers could potentially be avoided if PA levels increased to higher PA levels (5-10 in the scale) 150 minutes per week.

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7 **78 Introduction**

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9 79 Endometrial cancer is the sixth most common cancer, and the most frequent gynecologic
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11 80 malignancy among women in Norway. In 2014, 727 new cases were diagnosed and 81
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13 81 women died of the disease [1]. Established risk factors for endometrial cancer include use of
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15 82 exogenous estrogens unopposed by progestagens, early menarche (10-12 years of age), late
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17 83 menopause, nulliparity, diabetes mellitus, and obesity. Currently, the majority of endometrial
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19 84 cancer, and about half of the cases in postmenopausal women are attributable to being
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21 85 overweight or obese [2-4]. As the population ages and the prevalence of overweight, obesity,
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23 86 and sedentary lifestyle increase, the incidence of endometrial cancer is also expected to
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25 87 increase, especially in postmenopausal women [5, 6]. Thus primary prevention of endometrial
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27 88 cancer through modifiable lifestyle factors is of potential public health importance.

28 89 Physical activity (PA) is a modifiable lifestyle factor, which is important in the regulation
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30 90 of hormones and metabolic pathways. It is also associated with weight control, and thus may
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32 91 reduce endometrial cancer risk [7-9]. A pooled analysis of nine cohorts from Europe and the
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34 92 United States included 1.44 million participants and found a 21% reduced risk of endometrial
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36 93 cancer associated with recreational PA [10]. However, within individual studies, results are
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38 94 inconsistent [8]. For example, the Women's Health Study did not find any relationship
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40 95 between recreational PA and walking and endometrial cancer risk [11]. Similarly, there was
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42 96 no significant association between total PA – including occupational, recreational, and
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44 97 household-related PA – and endometrial cancer risk in the European Prospective Investigation
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46 98 into Nutrition and Cancer [12]. The 2007 evaluation by the World Cancer Research
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48 99 Fund/American Institute for Cancer Research (WCRF/AICR) concluded that there is a
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50 100 probable relationship between PA and endometrial cancer despite the variety of PA
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52 101 assessments not allowing for meta-analysis on dose-response [7]. This conclusion was
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54 102 supported in their Continuous Update Project (CUP) report from 2013 [8]. Of four cohort

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7 103 studies published after the 2013 CUP report [10, 13-15], three found an inverse association
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9 104 between recreational PA and endometrial cancer risk [10, 15, 14], and one did not [13].

10 105 Few studies have investigated the association between endometrial cancer and PA using a
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12 106 total and repeated measure of PA and different subtypes of endometrial cancer [12, 16, 17].
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14 107 Endometrial cancer is classified as type I (estrogen dependent), which constitutes the majority
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16 108 of cases (about 80%), and type II (estrogen independent), based on clinical, endocrine, and
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18 109 epidemiological observations. The most common histological subtypes of endometrial cancer
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20 110 are endometrioid carcinoma, serous carcinoma, carcinosarcoma, and clear cell carcinoma
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22 111 [18]. While the association between body mass index (BMI) and endometrial cancer is well
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24 112 established, the relationship between PA and endometrial cancer in women with different
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26 113 body sizes remains unclear.

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28 114 The present study aimed to investigate the association between endometrial cancer and PA
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30 115 level at two points in time in women with different BMI profiles in the Norwegian Women
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32 116 and Cancer (NOWAC) Study, and to calculate the population attributable fraction (PAF) of
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34 117 endometrial cancer for low PA levels.

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7 120 **Methods**

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9 121 **The NOWAC Study**

10 122 The NOWAC Study is a nationally representative cohort study that has been described in
11 123 detail previously [19, 20]. Briefly, random samples of Norwegian women aged 30-70 years
12 124 were invited to participate during three waves of data collection (1991/92, 1996/97, and
13 125 2003/04) [20]. More than 172,000 women completed a questionnaire with detailed questions
14 126 regarding lifestyle, diet, and health, and were enrolled in the study (overall response rate:
15 127 52.7%). The NOWAC Study was approved by the Regional Committee for Medical Research
16 128 Ethics and the Norwegian Data Inspectorate, and all participants included in the study gave
17 129 written informed consent.

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20 130 In this analysis we used information from enrollment questionnaires completed in the
21 131 period from 1996 to 2004 (baseline), and those with follow-up questionnaires completed 6-8
22 132 years after enrollment. In total 101,321 women completed questionnaires in these periods and
23 133 were eligible for inclusion in this study. We excluded women with prevalent cancers other
24 134 than non-melanoma skin cancer at baseline (n=4,454), those who emigrated or died before the
25 135 start of follow-up (n=20), those with hysterectomy (n=5,426), and those who had missing
26 136 information on PA level at baseline (n=8,662). Thus, the final analytical study sample
27 137 consisted of 82,759 women. Follow-up information on PA level, smoking, weight, and height
28 138 was available for for 52,370 (63.3%) of these women.

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45 140 **Assessment of PA level and covariates**

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47 141 PA level was assessed in the NOWAC questionnaires on a 10-point scale by the following
48 142 question: *“By physical activity we mean activity both at work and outside work, at home, as
49 143 well as training/exercise and other physical activity, such as walking, etc. Please mark the
50 144 number that best describes your level of physical activity; 1 being very low and 10 being very
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7 145 *high*". This PA scale has been validated [21] and refers to the total amount of PA across
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9 146 different domains, including recreation, occupation, transportation, and household in one
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11 147 global score. Moderate, but significant Spearman's rank correlation coefficients were found
12
13 148 (range: 0.36-0.46; $P < 0.001$) between PA level at enrollment and concurrent outcomes from
14
15 149 criterion measures of a combined sensor monitoring heart rate and movement. ~~This~~
16
17 150 ~~corresponded to mean values of 0.8 (very low) and 3.4 hours per day (very high) of~~
18
19 151 ~~moderate/vigorous PA, respectively, with a linear increase (P for trend < 0.001).~~ The PA scale
20
21 152 appeared valid to rank PA level in Norwegian women, but not to quantify a definite dose of
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23 153 PA [21].

24 154 Information on the covariates height, weight, age at menarche, parity, oral contraceptive
25
26 155 use, menopausal status, age at menopause, hormone therapy use, years of education, smoking
27
28 156 status ~~and~~, alcohol consumption, were obtained from NOWAC questionnaires. ~~The women~~
29
30 157 ~~were as considered postmenopausal if they stated that the period had stopped or had a~~
31
32 158 ~~hysterectomy (excluded from the study) or reported use of hormonal therapy if they were~~
33
34 159 ~~≥ 53 years. This cut-off point is based on the definition used in the the Million Women Study~~
35
36 160 ~~[22], and has been used by the NOWAC study earlier [23].~~ Information on height and weight
37
38 161 was used to calculate BMI (kg/m^2).

41 163 **Cancer incidence, death, and emigration**

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43 164 Women diagnosed with a primary, invasive, malignant neoplasm of the endometrium
44
45 165 (International Statistical Classification of Diseases, Injuries and Causes of Death Revisions 7
46
47 166 ~~and 10~~ codes 172.0 ~~and C 54.1, respectively~~ [24]) were identified through linkage to the
48
49 167 Cancer Registry of Norway, from which date of diagnosis and morphology (International
50
51 168 Classification of Diseases for Oncology, 3rd edition) were also obtained. Based on the
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53 169 morphology, endometrial cancers were categorized into overall endometrial cancer (all
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7 170 subtypes), endometrioid carcinoma, type 1 endometrial cancer (adenocarcinoma NOS,
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9 171 endometrioid, and squamous carcinomas), and other subtypes (non-endometrioid or non-type
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11 172 1).

12 Information on date of death or emigration was obtained through linkage to the
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14 174 Norwegian National Population Register.

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17 176 **Statistical methods**

18 177 Analyses using baseline data only

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22 178 We used Cox proportional hazard regression models to calculate hazard ratios (HRs) with
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24 179 95% confidence intervals (CIs) comparing five categories of PA level (1-2, 3-4, 5-6, 7-8, and
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26 180 9-10). PA level 5-6 was set as the reference group. Follow-up time was defined as the interval
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28 181 between age at baseline and age at cancer diagnosis, death, emigration, or the end of follow-
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30 182 up (31 December 2013), whichever came first.

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32 183 Departures from the proportional hazards assumption in the Cox models were tested through
33
34 184 the inclusion of an interaction variable between categories of PA and underlying time (age). A
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36 185 preliminary analysis of baseline data only was used to select the covariates that were adjusted
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38 186 for in the final models. In the preliminary model, we adjusted for: height (in metres), BMI
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40 187 (normal weight: <25 , overweight: $25-29.9$, obese: ≥ 30 kg/m²), age at menarche (<12 , 13-14,
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42 188 15+ years), parity (0, 1, 2, 3, 4+), oral contraceptive use (ever/never), menopausal status
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44 189 (premenopausal, perimenopausal, postmenopausal, hormone therapy use ≥ 53 years),
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46 190 hormone therapy use (ever/never), years of education (≤ 9 , $>9-12$, ≥ 13 years), smoking status
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48 191 (never, former, current), alcohol consumption (grams per day), and diabetes mellitus (yes/no).

49 192 The removal of each covariate had to be associated with a change in the regression
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51 193 coefficients of at least 10% in any of the categories of PA level to be included in the final
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53 194 model. To test for linear trend, we used the original, 10-point PA scale, modelled as a

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7 195 continuous variable in the analyses. Interactions (log likelihood test) between PA and the
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9 196 above-mentioned categories of BMI, educational attainment and smoking status were tested.
10 197 The Wald χ^2 statistic was used to test for heterogeneity between normal weight and obese
11
12 198 women, not significant.

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14 199 ~~As BMI is a strong risk factor for endometrial cancer, we decided to investigate the~~
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16 200 ~~association between PA and endometrial cancer risk in normal weight, overweight, and obese~~
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18 201 ~~women, even though the interaction term was not significant (p=0.49). The Wald χ^2 statistic~~
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20 202 ~~was used to test for heterogeneity between normal weight and obese women.~~

21 22 203 23 24 204 Analyses using repeated PA measurements

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26 205 We used the method proposed by Hu et al [25], i.e., baseline data was used until follow-up
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28 206 information became available, death, or emigration, whichever occurred first. Thereafter
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30 207 follow-up information was applied until death, emigration, or the end of the study period,
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32 208 which ever occurred first. In the analysis using repeated PA measurements, we also used
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34 209 follow-up information on BMI and smoking once it became available.

35 210 36 37 211 Complementary analysis - multiple imputation

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39 212 Compared to women who did not drop out of the study, those who dropped out of the study at
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41 213 follow-up (n=30,389 (36.7%)), were more often overweight (31.4% vs 29.2%) or obese
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43 214 (10.3% vs 8.6%), more often reported oral contraceptive use (46.6% vs 43.5%) and hormone
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45 215 therapy use (36.7% vs 31.7%), more often had a history of diabetes mellitus (2.9% vs 1.7%),
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47 216 and had fewer years of education (24.3% vs 23.7%). They were also more often current
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49 217 smokers, but on average they had a similar PA level and alcohol consumption as women who
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51 218 did not drop out of the study. In order to deal with dropouts, we used multiple imputation
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53 219 models [26] and compared the results with those of complete-case analyses. Multiple

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7 220 imputation models were used under the assumption that data was missing at random. To
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9 221 reduce sampling variability, we created 20 replicate datasets from the imputation simulation
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11 222 [27]. We used the outcomes overall endometrial cancer, type 1 endometrial cancer, and
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13 223 endometrioid carcinoma. Nelson-Aalen cumulative hazard estimator was included as a
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15 224 predictor in the imputation models [28]. The estimates from the 20 imputed datasets were
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17 225 combined using Rubin's rules [29]. All the analyses and multiple imputations were done in
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19 226 STATA version 14.0 (Stata Corp, College Station, TX, USA).
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22 228 PAF calculation

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24 229 We calculated the PAF to estimate the proportion of endometrial cancer that could be avoided
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26 230 in the population if women had different PA levels, using the formula: $PAF = Pe * (RRe -$
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28 231 $1) / [Pe * RR + (1 - Pe)]$, where Pe is the proportion of PA level in the study population and RRe is
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30 232 the RR in the model adjusting for BMI (model 1) and the final baseline multivariable
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32 233 proportional hazards regression model (model 2), including all aforementioned confounders
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34 234 and BMI. We calculated two-sided 95% CIs for the PAFs using the PUNAF Stata module
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36 235 [30]. The PA levels were divided into two levels: levels 1 to 4 were classified as exposed to
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38 236 low PA levels and levels 5-10 as unexposed to low PA levels. The PAF was interpreted as the
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40 237 proportion of overall endometrial cancers that would not occur in the average population if
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42 238 PA levels waswere between 5 and 10 according to the scale. ≥ 8 , corresponding to 150 minutes
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44 239 per week according to the validation of PA in NOWAC, assuming that the distribution of the
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46 240 adjustment variables remained unchanged.
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243 Results

244 The median age at baseline was 51 years. During a mean follow-up time of nearly 13 years,
245 687 cases of endometrial cancer were identified, with type 1 endometrial cancer
246 (adenocarcinoma not otherwise specified [NOS], endometrioid and squamous carcinoma)
247 accounting for 83.8% of the cases. The age at diagnosis ranged between 42 and 86 years, with
248 a mean of 62 years of age. Nearly half (43%) of the women reported a PA level between 5
249 and 6 (Table 1), and collapsing the upper part of the scale showed that a Approximately 74%
250 of the women reported a PA level between 5 and 10, with level ≥ 8 comprised 15% of the
251 participants. Women with a PA level >5 had a lower BMI, used less hormone therapy,
252 reported less diabetes mellitus, and were more often never smokers compared to women
253 reporting low PA levels. (Table 1).

254 Multivariable models of the associations between baseline and one follow-up
255 measurement of PA and endometrial cancer risk shows that compared to women with a PA
256 level of 5-6, those with a PA level of 1-2 had a 60% higher risk of overall endometrial cancer
257 (HR=1.60, 95% CI 1.16-2.20). Removing BMI from the models increased these estimates
258 (HR=1.85, 95% CI 1.36-2.36). For analyses using repeated PA measurements, the
259 corresponding risks adjusted for BMI and smoking status were similar to those obtained when
260 using baseline data only (HR with BMI adjustment=1.54, 95% CI 1.01-2.17 and HR without
261 BMI adjustment=1.80, 95% CI 1.19-2.72). In analyses using baseline data only and those
262 using repeated PA measurements, BMI and smoking status were negatively associated with the
263 risk of type 1 endometrial cancer and endometrioid carcinomas. Compared to the age-
264 adjusted models, the associations were attenuated in the multivariable adjusted models that
265 included BMI (Table 2).

266 Interactions between PA and categories of BMI, educational attainment and smoking
267 status were not significant. However, a As BMI is a strong risk factor for endometrial cancer,

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7 268 we decided to investigate the association between PA and endometrial cancer risk in normal
8 weight, overweight, and obese women, even though the interaction term was not significant
9 (p=0.49). When analyses were stratified by BMI category the PA levels 7-10 were collapsed,
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11 PA was not associated with overall endometrial cancer among normal-weight women in
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13 analyses using baseline data only ($HR_{PA(1-2) \text{ vs } (5-6)}=1.32$, 95% CI 0.71-2.45). The
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15 corresponding association in obese participants was $HR_{PA(1-2) \text{ vs } (5-6)}=3.08$ (95% CI 1.76-5.39)
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17 ($p_{\text{heterogeneity}}=0.05$) (Table 3).
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20 275 Using multiple imputation, we found that the estimates at all levels of adjustment and for
21
22 276 all endpoints (overall endometrial cancer, type 1 endometrial cancer, and endometrioid
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24 277 carcinoma) were consistent with those obtained from the complete-case analyses (Table 4).
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26 278 ~~(Supplemental Table 1)~~. PAF calculations showed that if women with a PA level ≤ 4 increased
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28 279 ~~to levels 5-10 in the scale that level to ≥ 8 , 21.934%~~ (95% CI: ~~7.16-34.349~~) of endometrial
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30 280 cancers could be avoided (Table 5). ~~PAF calculations based on the proportional hazards~~
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32 281 ~~regression model including BMI yielded a lower proportion (17%, 95% CI: 2.3-29.5) (Table~~
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34 282 ~~5). The results did not differ substantially for subtypes of endometrial cancer (Supplemental~~
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36 283 ~~table 1) (more than 1 in 4) (Supplementary Figure 1).~~
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39 285 Discussion

40 286 In this large Norwegian cohort we found an inverse dose-response association between PA
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42 287 and endometrial cancer overall, type 1 endometrial cancer, and endometrioid carcinoma. The
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44 288 results were consistent when using baseline data on PA and when using repeated PA
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46 289 measurements, as well as when multiple imputation was used. Our findings further suggest
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48 290 that the association between PA and endometrial cancer is independent of BMI, as risk
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50 291 estimates were attenuated, but still significant, when BMI was incorporated in the statistical
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52 292 models. Stratification by BMI category indicated that the risk of low PA on endometrial
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54 293 cancer was statistically significant among obese women only (although the test for interaction
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7 294 | was not statistically significant, $p=0.49$). Among women with PA levels ≤ 4 , 21.931% of
8 295 | endometrial cancer could potentially be avoided if these women adopted a PA level between
9 296 | 5-10 in the scale ≥ 8 , which corresponds to approximately 150 minutes of moderate/vigorous
10 296 | PA per week.
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14 298 | Other cohort studies investigating the association between total PA levels – which include
15 298 | domains such as recreation, occupation, transportation, and household – and endometrial
16 299 | cancer are sparse; most studies measured recreational PA only and few studies use repeated
17 300 | measurements of PA. In contrast to our results, the European Prospective Investigation into
18 301 | nutrition and Cancer reported a non-significant trend (p-trend 0.36) for total PA (including the
19 302 | domains recreation, occupation, and household) when comparing active with inactive women
20 303 | (multivariable adjusted model including BMI: HR=0.88, 95% CI 0.61-1.27) [12]. This was
21 304 | similar for the Breast Cancer Detection Demonstration Project study, which measured the
22 305 | total intensity of PA and found no significant associations with endometrial cancer [31].
23 306 | Findings from the Netherlands Cohort Study on Diet and Cancer showed that total baseline
24 307 | non-occupational PA was inversely associated with endometrial cancer, with a lower risk
25 308 | observed for a PA corresponding to >30 minutes per day [17, 32]. In a Swedish cohort the
26 309 | risk was decreased, although this decrease was not significant [16].
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39 311 | Several studies have reported on recreational PA and endometrial cancer. Nine
40 312 | prospective cohort studies on recreational PA were included in the WCRF/AICR CUP report
41 313 | up to 2012 [8], but due to different measures of PA, the meta-analysis of these studies only
42 314 | looked at the highest vs lowest PA level (RR=0.73, 95% CI 0.58-0.93), and these results were
43 315 | attenuated when the model was adjusted for BMI (RR=0.80, 95% CI 0.69-0.92). A limitation
44 316 | of this meta-analysis was the high heterogeneity ($I^2=75.9\%$) of the individual studies [8].
45 317 | Indeed, only three of these studies [33, 32, 34] found significant inverse associations, three
46 318 | found no significant association [35, 11, 36], and three [37, 12, 16] found an inverse, but
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7 319 insignificant association between endometrial cancer and recreational PA. Since the
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9 320 publication of the WCRF/AICR CUP report from 2012 we have identified four additional
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11 321 prospective cohort studies on recreational PA and endometrial cancer [10, 13-15]. The
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13 322 Nurses' Health study investigated recreational PA in the past year and found no association
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15 323 between baseline recreational PA and endometrial cancer risk, however, brisk walking time
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17 324 ≥ 3 hours per week was inversely associated with endometrial cancer [15]. In the California
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19 325 Teachers Study cohort, moderate and vigorous recreational PA was associated with a 25%
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21 326 lower endometrial cancer risk [13]. The findings of Land et al [14] are in accordance with our
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23 327 findings, although they studied recreational PA and had a small number of cases in a
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25 328 population of women at high risk for breast cancer. A large pooled analysis of 12 cohorts was
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27 329 recently published and reported a HR of 0.79 (95% CI 0.68-0.92) in the association between
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29 330 recreational PA and endometrial cancer based on 5346 cases. However, the degree of
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31 331 heterogeneity between cohorts was high ($I^2=69\%$)[10] .

32 332 Analysis of occupational PA measured twice during 1974 and 1981 in a Norwegian study
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34 333 showed a significant trend, with a reduced risk for women who were consistently moderately
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36 334 active; however, the association was attenuated in the multivariable model and the trend was
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38 335 no longer significant [36]. The WCRF/AICR CUP report [8] included four cohort studies [16,
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40 336 38, 12, 39], none of which found a significant association between occupational PA and
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42 337 endometrial cancer. In a highest vs lowest occupational PA meta-analysis, the summary RR
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44 338 was 0.79 (95% CI 0.71-0.88), with a high degree of heterogeneity between studies ($I^2=$
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46 339 75.9%) and concluded a probable inverse association between occupational PA and
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48 340 endometrial cancer [8].

49 341 Overweight and obesity are strong risk factors for endometrial cancer, and studies suggest
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51 342 that the association between PA and endometrial cancer is either mediated or confounded by
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53 343 body weight, which can affect hormone profiles. Therefore, it is important to model the
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7 344 association both with and without adjustment for BMI [15]. In our study, adjustment for BMI
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9 345 in the multivariable analyses attenuated the associations. However, a modest inverse
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11 346 association remained, suggesting that PA is independently associated with endometrial
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13 347 cancer. Simultaneously, the analyses of the different BMI categories showed that the
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15 348 association was more pronounced in obese than in normal-weight women. In our data, obesity
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17 349 may confound the association between PA and overall endometrial cancer. Our findings are in
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19 350 accordance with Friberg et al [16]. However, Moore et al adjusted for BMI in the association
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21 351 between recreational PA and endometrial cancer and showed an attenuation of the estimates
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23 352 from a significant towards a non-significant result compared to multivariable models
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25 353 unadjusted for BMI (HR=0.98, 95% CI 0.89-1.09 vs HR=0.79, 95% CI 0.68-0.92) . This was
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27 354 similar to several previous studies [14, 15, 33, 37]. Some studies have found a statistically
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29 355 significant increased endometrial cancer risk in both inactive and active overweight women
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31 356 [11], which correspond to our findings. Others have shown an effect modification, where the
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33 357 inverse relationship was only seen among overweight or obese women [10, 37]. As in our
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35 358 study, several other studies have reported no significant effect modification for BMI [33, 12,
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37 359 16, 17, 31].

37 360 Heterogeneity in different study results may be explained by variations in the methods
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39 361 used to assess PA (self-administered questionnaires, interviews, or use of job titles); PA
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41 362 domains (recreation, occupation, transportation, household); frequency, duration, and
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43 363 intensity of PA; and time periods in life when PA was measured, as well as different statistical
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45 364 methods used in the data analysis [40]. Nevertheless, there is substantial biological evidence
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47 365 to support a potential protective role of PA on endometrial cancer. The mechanisms involved
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49 366 have been hypothesized as affecting endogenous sex hormone levels, insulin-mediated
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51 367 pathways, and maintenance of energy balance [41].
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7 368 Physical inactivity is considered an important risk factor for different cancers [42-44]. The
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9 369 consistent associations between low PA levels and endometrial cancer risk in our study
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11 370 justify the estimation of PAFs. Our definition of low PA levels was based on self-reported PA
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13 371 using a validated 10-point scale [21]. Our PAF estimation represents the minimum move
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15 372 required from low to higher levels of PA to create a significant change in the incidence of
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17 373 endometrial cancer (21.934%, 95% CI: 7.1-34.3). However, the definite dose cannot be
18
19 374 quantified and our results must be interpreted with caution. ~~which corresponded to an~~
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21 375 ~~increase in PA to 150 minutes of moderate/vigorous PA per week. This amount is in~~
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23 376 ~~accordance with World Health Organization Global Recommendations on PA for Health~~. In
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25 377 the UK, Parkin found a PAF for endometrial cancer of 3.8% attributable to exercising less
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27 378 than the minimum recommended amount [43]. The proportion related to inadequate PA in the
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29 379 UK in 2002 was 30% for endometrial cancer, however that compared the highest (≥ 60
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31 380 minutes) and lowest (< 30 minutes) PA levels, which gives a higher reference category than
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33 381 the recommendation of PA [45]. To quantify the PAF requires a realistic population
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35 382 distribution of the exposure of interest, which in our study is PA. We consider our cohort to
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37 383 be a nationally representative Norwegian cohort with a reliable population distribution of
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39 384 PA, and as such it should give a ~~more~~ robust estimate. Furthermore, it is valuable to evaluate
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41 385 the impact of different factors in cancer prevention, which is helpful in prioritizing cancer
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43 386 prevention and intervention strategies.

44 387 A major strength of our study is its prospective, population-based design, and the use of a
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46 388 high-quality, nationally ~~representative~~ cancer registration system to identify endometrial
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48 389 cancer cases [20]. The large sample size and representativeness of the Norwegian female
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50 390 population 30 to 70 years of age gives a unique opportunity to calculate robust PAF estimates.
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52 391 The PA scale has been validated [21] and correlated well with all-cause mortality rates [46].
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54 392 Furthermore, PA level, BMI, and smoking were re-assessed at follow-up. Self-reported BMI

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7 393 has been validated for the NOWAC study, indicating that there was a substantial agreement
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9 394 between self-reported and measured BMI values [47]. There was, however, a small but
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11 395 statistically significant under-reporting of weight, which would affect self-reported BMI; this
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13 396 tendency was largest among overweight and obese women [20, 47] . A survey of the PA
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15 397 levels in the adult population in Norway showed that 34% of women reached the national
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17 398 guidelines for PA [48]. This proportion is higher than in our study. The relatively large
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19 399 number of cases made it possible to investigate subtypes of endometrial cancer, however the
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21 400 proportion of type 2 endometrial cancer was too low to allow for separate analyses. Multiple
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23 401 imputation of missing data, in addition to complete-case analysis, confirmed our results. The
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25 402 PA assessment in ~~our~~ this study comprised all areas of PA, not only recreational PA. However,
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27 403 the total self-reported measure of PA cannot differentiate intensity, duration, and frequency of
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29 404 PA, nor the type of PA in our study, and given the self report of PA, measurement errors
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31 405 cannot be ruled out. However, measurement errors would likely lead to a non-differential bias
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33 406 and a potential underestimation of the true effect. The PA assessment used in this study may
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35 407 not apply to women in other countries. Moreover, the potential for residual confounding, in
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37 408 particular by BMI, remains.

37 409

39 410 **Conclusions**

41 411 Overall, we found an inverse dose-response association between PA and endometrial cancer
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43 412 with similar findings for subtypes of endometrial cancer. This risk was higher in obese
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45 413 women. Also, ~~21.934~~ 21.934% of the endometrial cancer cases ~~could be were~~ attributable to low
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47 414 levels of PA, and ~~more than 1 in 4 cases~~ could potentially be avoided if women attained a
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49 415 higher PA level ~~corresponding to 150 minutes per week or more.~~

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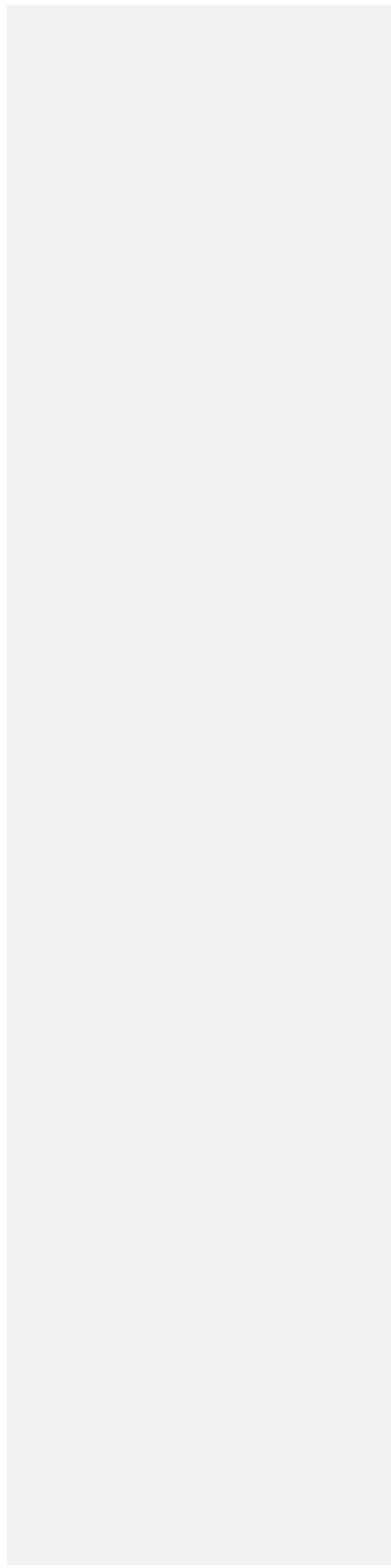
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418 **Ethical approval:** All procedures performed in studies involving human participants were in
419 accordance with the ethical standards of the institutional and/or national research committee
420 and with the 1964 Helsinki declaration and its later amendments or comparable ethical
421 standards.

For Peer Review



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Table 1 Selected baseline characteristics of participants in the Norwegian Women and Cancer Study by physical activity level (n=82,759)

Characteristic	Physical activity level				
	1 to 4 N=21,953 (26.5%)		5 to 10 N=60,806 (73.5%)		
	1 to 2 N=3855 (4.7%)	3 to 4 N=18,098 (21.9%)	5 to 6 N=35,551 (43.0%)	7 to 8 N=20,991 (25.4%)	9 to 10 N=4264 (5.2%)
Age (mean, ±SE)	53.2 (.11)	52.1 (.05)	51.5 (.03)	51.3 (.04)	51.9 (.10)
Person-years at risk ¹	48 995	236 571	462 837	266 512	54 318
Overall endometrial cancer (total cases n=687)	56 (8.2%)	181 (26.3%)	283 (41.2%)	139 (20.2%)	28 (4.1%)
Endometrioid (total cases n=473)	41 (8.7%)	134 (28.3%)	185 (39.1%)	100 (21.1%)	13 (2.7%)
Type 1 endometrial cancer ² (total cases n=576)	47 (8.2%)	161 (28.0%)	226 (39.2%)	122 (21.2%)	20 (3.5%)
Other subtypes ³ (total cases n=111)	9 (8.1%)	20 (18%)	57 (51.4%)	17 (15.3%)	8 (7.2%)
BMI (mean, ±SE)	26.9 (.09)	25.8 (.03)	24.6 (.02)	23.8 (.02)	23.6 (.05)
Missing (%)	2.2	2.0	1.7	1.7	2.2
Age at menarche (mean, ±SE)	13.2 (.03)	13.3 (.01)	13.3 (.007)	13.7 (.01)	13.4 (.02)
Missing (%)	1.6	1.6	1.4	1.2	1.7
Parity (%)					
Nulliparity	10.4	9.2	8.2	8.0	8.2
1-2	51.6	52.7	53.2	53.0	50.4
≥3	38.0	38.1	38.5	39.0	41.4
Ever use of oral contraceptives (%)	49.6	53.9	53.8	54.8	50.4
Missing (%)	3.9	2.9	2.8	3.2	4.3
Menopausal status (%)					
Premenopausal	38.4	47.4	50.0	48.8	44.4
Perimenopause	7.0	5.9	5.9	6.5	6.1
Postmenopausal	49.0	41.9	39.0	39.4	44.4
Hormonal therapy use <53 years	3.0	2.8	2.8	3.1	3.3
Missing	2.6	2.0	2.3	2.3	1.8
Ever use of hormonal therapy (%)	36.9	35.5	32.5	31.4	29.6
Missing (%)	2.8	2.4	2.6	2.4	3.4
Years of education (mean, ±SE)	11.5 (.06)	12.2 (.03)	12.3 (.02)	12.6 (.02)	11.9 (.06)

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Missing (%)	6.6	5.2	4.5	4.9	6.0
Smoking status (%)					
Never	29.6	36.1	37.3	37.4	35.2
Former	29.8	31.2	32.6	35.0	33.3
Current	39.1	31.4	28.9	26.3	30.0
Missing (%)	1.5	1.3	1.2	1.4	1.5
Alcohol consumption, mean ±SE (grams/day)	3.0 (.03)	3.4 (.03)	3.4 (.02)	3.5 (.03)	3.1 (.06)
Missing (%)	2.3	1.7	1.7	1.8	2.4
Diabetes mellitus (%)	4.4	2.1	1.6	1.3	1.6
Missing (%)	27.3	20.7	17.3	15.3	17.1

¹Total person years=1,069,232; average follow-up time 12.92 years (SD=3.65)
²Type 1 includes adenocarcinoma, endometrioid, squamous types
³Other subtypes are cases not equal to Type 1

Table 2 Relative risk estimates of endometrial cancer (overall, type 1, and endometrioid) by physical activity (PA) level at baseline and follow-up in the Norwegian Women and Cancer Study (n=82 759)

	Endometrial cancer	Models ^{1, 2, 3, 4}	1 to 2	3 to 4	5 to 6	7 to 8	9 to 10	p_trend
Baseline	Overall endometrial cancer	Crude n=687	1.73 (1.30-2.31)	1.21 (1.00-1.46)	1.00	0.87 (0.71-1.07)	0.83 (0.56-1.22)	0.00
		PA + BMI n= 673	1.47 (1.09-1.97)	1.09 (0.9-1.32)	1.00	0.91 (0.74-1.11)	0.86 (0.58-1.27)	0.01
		Multivariable without BMI n=607	1.85 (1.36-2.53)	1.28 (1.05-1.56)	1.00	0.89 (0.72-1.11)	0.71 (0.45-1.12)	0.00
		Multivariable n=593	1.60 (1.16-2.20)	1.15 (0.94-1.41)	1.00	0.92 (0.74-1.15)	0.73 (0.45-1.16)	0.01
	Type 1 endometrial cancer	Crude n=576	1.83 (1.33-2.51)	1.35 (1.10-1.65)	1.00	0.96 (0.77-1.19)	0.74 (0.47-1.17)	0.00
		PA + BMI n=564	1.51 (1.10-2.09)	1.20 (0.97-1.47)	1.00	1.01 (0.81-1.26)	0.76 (0.48-1.22)	0.01
		Multivariable without BMI n=510	1.97 (1.4-2.78)	1.47 (1.19-1.82)	1.00	1.00 (0.79-1.26)	0.68 (0.4-1.15)	0.00
		Multivariable n=498	1.66 (1.17-2.36)	1.31 (1.05-1.63)	1.00	1.04 (0.82-1.32)	0.69 (0.40-1.18)	0.00
	Endometrioid subtype	Crude n=473	1.96 (1.39-2.75)	1.37 (1.10-1.72)	1.00	0.96 (0.75-1.22)	0.59 (0.33-1.03)	0.00
		PA + BMI n=463	1.59 (1.12-2.25)	1.20 (0.96-1.51)	1.00	1.00 (0.79-1.29)	0.59 (0.33-1.06)	0.004
		Multivariable without BMI n=428	2.25 (1.57-3.22)	1.51 (1.2-1.91)	1.00	1.01 (0.78-1.3)	0.61 (0.33-1.13)	0.00
		Multivariable n=418	1.83 (1.26-2.64)	1.32 (1.04-1.67)	1.00	1.06 (0.82-1.37)	0.60 (0.32-1.15)	0.001
Repeated measurements PA	Overall	Crude n= 450	1.78 (1.22-2.58)	1.31 (1.04-1.65)	1.00	0.86 (0.67-1.10)	0.87 (0.54-1.40)	0.00
		PA + BMI n=438	1.48 (1.01-2.17)	1.18 (0.93-1.49)		0.91 (0.71-1.17)	0.98 (0.61-1.57)	0.04
		Multivariable without BMI n=393	1.80 (1.19-2.72)	1.35 (1.06-1.73)	1.00	0.92 (0.71-1.2)	0.71 (0.4-1.26)	0.00
		Multivariable n=381	1.54 (1.01-2.35)	1.22 (0.95-1.58)	1.00	0.97 (0.74-1.26)	0.80 (0.45-1.41)	0.02
	Type 1	Crude n = 387	1.98 (1.34-2.91)	1.39 (1.09-1.78)	1.00	0.83 (0.63-1.09)	0.93 (0.56-1.53)	0.00
		PA + BMI n=377	1.60 (1.08-2.39)	1.25 (0.97-1.61)	1.00	0.88 (0.67-1.17)	1.06 (0.64-1.75)	0.01

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		Multivariable without BMI n=337	2.10 (1.38-3.21)	1.46 (1.12-1.9)	1.00	0.94 (0.71-1.25)	0.8 (0.44-1.45)	0.00
		Multivariable n=327	1.75 (1.13-2.71)	1.33 (1.01-1.74)	1.00	0.99 (0.74-1.33)	0.91 (0.5-1.65)	0.01
	Endometrioid	Crude n = 321	1.90 (1.24-2.89)	1.30 (1.00-1.70)	1.00	0.72 (0.53-0.97)	0.61 (0.32-1.16)	0.00
		PA + BMI n=311	1.55 (1.00-2.39)	1.18 (0.9-1.55)	1.00	0.76 (0.55-1.03)	0.7 (0.37-1.34)	0.01
		Multivariable without BMI n=290	2.15 (1.38-3.34)	1.34 (1.01-1.79)	1.00	0.78 (0.57-1.07)	0.65 (0.33-1.28)	0.00
		Multivariable n=280	1.77 (1.12-2.81)	1.22 (0.91-1.63)	1.00	0.82 (0.60-1.14)	0.75 (0.38-1.49)	0.01

¹ Crude model with age as time-variable.
² Model with adjustment for BMI.
³ Multivariable model adjusted for use of hormone therapy, oral contraceptive use, years of education, smoking, alcohol consumption (gram per day).
⁴ Multivariable model same as above, but with adjustments for BMI included.
 BMI: body mass index

Table 3 Relative risk estimates of overall endometrial cancer by physical activity (PA) level at baseline and follow-up according to body mass index (BMI) status at baseline in the Norwegian Women and Cancer study (n=82,759)

Complete case models	Model ^{1,2}	BMI	1 to 2	3 to 4	5 to 6	7 to 10	p_trend
Baseline	Crude	Normal BMI n=318	1.28 (0.74-2.21)	1.06 (0.79-1.42)	1.00	0.83 (0.64-1.07)	0.10
		Overweight n=234	1.04 (0.60-1.83)	1.02 (0.75-1.39)	1.00	0.90 (0.64-1.26)	0.66
		Obese n=121	2.50 (1.49-4.20)	1.45 (0.92-2.29)	1.00	1.32 (0.74-2.36)	0.01
	Multivariable	Normal BMI n=281	1.32 (0.71-2.45)	1.19 (0.87-1.62)	1.00	0.86 (0.66-1.14)	0.07
		Overweight n=212	0.95 (0.51-1.77)	1.00 (0.73-1.39)	1.00	0.90 (0.63-1.28)	0.76
		Obese n=100	3.08 (1.76-5.39)	1.55 (0.93-2.56)	1.00	0.98 (0.48-1.99)	0.00
Repeated measurements PA	Crude	Normal BMI n=182	1.26 (0.58-2.73)	0.85 (0.56-1.30)	1.00	0.80 (0.58-1.12)	0.39
		Overweight n=169	1.44 (0.74-2.82)	1.39 (0.97-2.01)	1.00	1.16 (0.78-1.71)	0.61
		Obese n=87	1.78 (0.94-3.37)	1.39 (0.84-2.30)	1.00	0.73 (0.34-1.56)	0.01
	Multivariable	Normal BMI n=164	1.17 (0.47-2.91)	0.90 (0.58-1.41)	1.00	0.86 (0.61-1.21)	0.53
		Overweight n=147	1.15 (0.52-2.53)	1.35 (0.92-2.00)	1.00	1.17 (0.78-1.77)	0.81
		Obese n=70	2.45 (1.22-4.91)	1.63 (0.92-2.89)	1.00	0.56 (0.21-1.50)	0.00

¹ Crude model with age as time-variable.

² Multivariable model adjusted for use of hormone therapy, oral contraceptive use, years of education, smoking, alcohol consumption (gram/day).

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Table 4: Relative risk estimates of endometrial cancer (overall, type 1 and endometrioid) by physical activity (PA) level at baseline and follow-up with imputation for missing variables in the Norwegian Women and Cancer study (n=82,759)

Imputation	Models ^{1,2,3,4}	1 to 2	3 to 4	5 to 6	7 to 8	9 to 10	p_trend
Overall	Crude n=687	1.76 (1.27-2.44)	1.34 (1.09-1.65)	1.00	0.80 (0.65-1.00)	0.73 (0.48-1.12)	0.00
	PA + BMI n= 687	1.47 (1.05-2.05)	1.22 (0.98-1.50)	1.00	0.85 (0.69-1.06)	0.80 (0.52-1.22)	0.001
	Multivariable without BMI n=687	1.87 (1.32-2.63)	1.40 (1.13-1.74)	1.00	0.85 (0.69-1.07)	0.71 (0.45-1.13)	0.02
	Multivariable n=687	1.58 (1.11-2.24)	1.28 (1.02-1.59)	1.00	0.90 (0.72-1.13)	0.78 (0.49-1.22)	0.02
Type 1	Crude n=576	1.87 (1.23-2.83)	1.30 (1.00-1.70)	1.00	0.71 (0.53-0.96)	0.60 (0.31-1.14)	0.00
	PA + BMI n= 576	1.51 (0.99-2.31)	1.16 (0.89-1.52)	1.00	0.77 (0.57-1.04)	0.67 (0.35-1.27)	0.001
	Multivariable without BMI n=576	2.05 (1.34-3.15)	1.34 (1.02-1.77)	1.00	0.77 (0.57-1.05)	0.66 (0.35-1.27)	0.00
	Multivariable n=576	1.66 (1.08-2.57)	1.19 (0.90-1.58)	1.00	0.83 (0.61-1.13)	0.74 (0.39-1.42)	0.002
Endometrioid	Crude n=473	1.89 (1.28-2.79)	1.45 (1.13-1.85)	1.00	0.76 (0.58-0.99)	0.48 (0.24-0.96)	0.00
	PA + BMI n= 473	1.51 (1.01-2.26)	1.28 (1.00-1.64)	1.00	0.82 (0.63-1.07)	0.54 (0.27-1.08)	0.01
	Multivariable without BMI n=473	2.11 (1.42-3.14)	1.53 (1.18-1.97)	1.00	0.83 (0.63-1.09)	0.54 (0.27-1.07)	0.00
	Multivariable n=473	1.70 (1.13-2.56)	1.35 (1.05-1.75)	1.00	0.89 (0.68-1.17)	0.60 (0.30-1.20)	0.00

¹ Crude model with age as time-variable.

² Model with adjustment for BMI.

³ Multivariable model adjusted for use of hormone therapy, oral contraceptive use, years of education, smoking, alcohol consumption (gram per day).

⁴ Multivariable model same as above, but with adjustment for BMI included.

BMI: body mass index

Table 5: Population attributable fraction (PAF) for the proportion of endometrial cancer in the population that would be avoided if low physical activity (PA) level increased

	Pe	Overall					
		Model 1 ¹ n= 673			Model 2 ² n= 593		
PA level	Pe	PAF	PAF 95% CI	RR= 95% CI	PAF	PAF 95% CI	RR= 95% CI
[1-4] to [5-10]	26.5 %	17%	[2.3-29.5]	1.21 [1.02-1.42]	21.9%	[7.1-34.3]	1.28 [1.08-1.52]

¹Model 1: measured at baseline with age as time variable and adjusted for BMI.

²Model 2: Measured at baseline in a multivariable model adjusted for BMI, oral contraceptive use, hormone therapy use, years of education, smoking status, and alcohol consumption (grams per day).

Pe: proportion of low physical activity levels, RR: relative risk, CI: confidence interval