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Risk of lung cancer and physical activity in smokers and non-smokers, the Norwegian Women and Cancer Study

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Corresponding Author:	Kristin Benjaminsen Borch, PhD University of Tromsø Tromsø, NORWAY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Tromsø
Corresponding Author's Secondary Institution:	
First Author:	Kristin Benjaminsen Borch, PhD
First Author Secondary Information:	
Order of Authors:	Kristin Benjaminsen Borch, PhD
	Elisabete Weiderpass, MD, PhD
	Tonje Braaten, PhD
	Merethe Selnes Hansen, MD
	Idlir Licaj, PhD
Order of Authors Secondary Information:	
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Risk of lung cancer and physical activity in smokers and non-smokers, the Norwegian Women and Cancer Study

Kristin Benjaminsen Borch[1*], Elisabete Weiderpass[1, 2, 3, 4], Tonje Braaten[1], Merethe Selnes Hansen[1], Idlir Licaj[1]

*Corresponding author: Kristin Benjaminsen Borch, email: Kristin.benjaminsen.borch@uit.no

Phone: +47 77645443, ORCID id: orcid.org/0000-0002-1741-2322

Affiliations:

1. Department of Community Medicine, Faculty of Health Sciences, UiT, The Arctic University of Norway, Tromsø, Norway
2. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
3. Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway
4. Genetic Epidemiology Group, Folkhälsan Research Centre, Samfundet Folkhälsan, Helsinki, Finland

Abstract

We aimed to investigate physical activity (PA) and risk of different histological subtypes of lung cancer according to smoking status and to take advantage of repeated measurements of PA and smoking status in a large cohort of women in Norway. The study sample for the baseline data only analysis consisted of 80,802 women. Repeated measurements of PA level, smoking, weight, and height were available for 54,691 women (63.2%), who were included in repeated measurement analyses combined with multiple imputation to address attrition. Cox proportional hazard regression models were used to calculate hazard ratios with 95% confidence intervals. During a median follow-up of 12.9 years, 782 cases of primary lung cancer were identified. We found an inverse dose-response association between PA and lung cancer overall. The results were consistent when using baseline data and repeated measurements of PA and possible confounders. We observed a similar trend for adenocarcinoma, but not for squamous cell or small cell carcinomas. Our findings suggest a more pronounced association between lung cancer and PA levels in current and former smokers, and in normal-weight and overweight participants with increasing PA levels.

Keywords: Lung cancer; physical activity; smoking; prospective study; women

Introduction

Lung cancer incidence has been increasing among women. In Norway, it is the third most common cancer among women, accounting for 9% of all cancers, with 1,471 new cases diagnosed in 2015 [1]. Lung cancer is one of the most incurable cancers due to late presentation and disease recurrence with high fatality [2]. Five-year relative survival for lung cancer is low and was 19.2 % for women in 2010-2014 [1].

Smokers are 14 times more likely to develop lung cancer compared to non-smokers [3]. However, not all smokers develop lung cancer, suggesting individual variability in susceptibility to smoke-related respiratory carcinogens [3]. In 2002, the International Agency of Research in Cancer concluded that the association between physical activity (PA) and risk of lung cancer remained inconclusive [4]. In the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report from 2007, the evidence for a protective effect of PA on lung cancer was categorized as limited [5]. However, in the years that followed, several meta-analyses concluded that there was an association between recreational PA and a reduced risk of lung cancer [6-10, 3, 11]. Moreover, it has been suggested that the association between PA and risk of lung cancer among smokers is stronger in women than men [3]. The WCRF/AICR report included different domains of PA, but few studies have investigated both baseline and repeated measurements of PA and other lifestyle factors [5].

It is still unclear whether the association between PA and lung cancer is the result of an oversimplification of lifetime smoking; and therefore a better understanding of this association in never smokers is needed, particularly for women. Indeed, few studies to-date have investigated the association between PA and lung cancer in never smokers, and those that did found no statistically significant association [12-16].

We aimed to investigate PA and risk of different histological subtypes of lung cancer according to smoking status and to take advantage of repeated measurements of PA and smoking status in a large cohort of women in Norway.

Methods

The Norwegian Women and Cancer Study

The Norwegian Women and Cancer (NOWAC) Study is a nationally representative cohort study that has been described in detail previously [17]. Briefly, random samples of Norwegian women aged 30-70 years were invited to participate during three waves of data collection (1991/92, 1996/97, and 2003/04) [17, 18]. More than 172,000 women were enrolled in the study and completed a questionnaire with detailed questions regarding lifestyle, diet, and health, with an overall response rate of 52.7%. The NOWAC Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate, and all participants included in the study gave written informed consent.

In this analysis we used information from enrollment questionnaires completed in 1996-2004 (baseline), and from follow-up questionnaires completed 6-8 years after enrollment (repeated measurement). In total 101,321 women completed baseline questionnaires and were eligible for inclusion in this study. We excluded women with prevalent cancers other than non-melanoma skin cancer at baseline (n=4,450), those who emigrated or died before the start of follow-up (n=13), and those who had missing information on PA level at baseline (n=9,208), smoking status (n=1,151), or other main covariates (n=5,697). Thus, the final analytical study sample for analyses using baseline data only consisted of 80,802 women. Repeated measurements of PA level, smoking, weight, and height were available for 54,691 (63.2%) of these women, who were included in the corresponding analyses.

Data collection

The description and validation of the assessment of PA in the NOWAC Study have been described elsewhere [19]. Briefly, respondents reported their PA in the NOWAC questionnaire on a 10-point scale after reading the following explanation: *"By physical activity we mean activity both at work and outside work, at home, as well as training/exercise and other physical activity, such as walking, etc. Please mark the number that best describes your level of physical activity; 1 being very low and 10 being very high".* The scale therefore reflects the amount of PA across different domains, including recreational, occupational, transportation, and household PA, and combines them into one global PA level. This PA scale appeared valid to rank PA level in Norwegian women, but not to quantify a definite dose of PA [19]. Information on the covariates height, weight, years of education, smoking status, alcohol consumption, fruit consumption, and vegetable consumption were taken from the NOWAC questionnaire. Information on height and weight was used to calculate body mass index (BMI, kg/m^2).

Women diagnosed with a primary, invasive, malignant neoplasm of the lung (International Statistical Classification of Diseases, Injuries and Causes of Death Revision 10 codes C33-34) [20] were identified through linkage to the Cancer Registry of Norway, from which date of diagnosis and morphology (International Classification of Diseases for Oncology, 3rd edition) were also obtained. Based on morphology, lung cancers were categorized into adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, other non-small cell carcinoma, and other or not otherwise specified carcinoma. Here we present data on the risk of lung cancer overall and on adenocarcinoma, squamous cell carcinoma, and small cell carcinoma, as they were the most frequent subtypes of lung cancer. Information on date of death or emigration was obtained through linkage to the Norwegian National Population Register.

Statistical methods

Analyses using baseline data only

We used Cox proportional hazard regression models to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) comparing five categories of PA level (1-2, 3-4, 5-6, 7-8, and 9-10). PA level 5-6 was set as the reference group. Follow-up time was defined as the interval between age at baseline and age at cancer diagnosis, death, emigration, or the end of follow-up (31 December 2014), whichever came first.

Departures from the proportional hazards assumption in the Cox models were tested through the inclusion of an interaction variable between categories of PA level and underlying time (age) [21]. A preliminary analysis of baseline data was used to select the covariates for which we adjusted in the final models. The covariates that led to a change of at least 10% in the PA regression coefficient were: BMI (normal weight: <25, overweight: 25–29.9, obese: ≥30 kg/m^2), years of education (≤9, 9-12, ≥13 years), smoking status (never, former, current), and fruit consumption in quartiles. To test for linear trend, we used the original, 10-point PA scale, modelled as a continuous variable in the analyses. Interactions (log likelihood tests) between PA and the above-mentioned categories of BMI, years of education, and smoking status were tested. In the stratified analyses, PA levels 7-10 were collapsed both in baseline and repeated measurements analyses due to the low number of participants in the separate groups.

Analyses using repeated PA measurements

We used the method proposed by Hu et al [22], i.e., baseline data was used until follow-up information became available, death, or emigration, whichever occurred first. Thereafter, follow-up information was applied until death, emigration, or the end of the study period, which ever occurred first. In the analysis using repeated PA

measurements, we also used follow-up information on BMI, smoking status, and fruit consumption once it became available.

Complementary analysis – chained multiple imputation

Women who dropped out of the study were more often current smokers, but on average they had PA levels that were similar to those of women who did not drop out of the study. In order to deal with dropouts, we used chained multiple imputation models [23] and compared the results with those of baseline analyses. Chained multiple imputation models were used under the assumption that data was missing at random. To reduce sampling variability, we created 20 replicate datasets from the imputation simulation [24]. We used the outcomes lung cancer overall, adenocarcinoma, squamous cell carcinoma, and small cell carcinoma. The Nelson-Aalen cumulative hazard estimator was included as a predictor in the imputation models [23]. The estimates from the 20 imputed datasets were combined using Rubin's rules [25]. Similar statistical analyses combining repeated measurements with multiple imputation have been described in previous publications [26, 27]. All the analyses and multiple imputations were done in STATA version 14.0 (Stata Corp, College Station, TX, USA).

Results

During more than 1.1 million person-years and a median follow-up of 12.9 years, 782 cases of primary lung cancer were identified. There were 353 (45.1%) adenocarcinomas 45%, 112 (14.3%) squamous cell carcinomas, and 146 (18.7%) small cell carcinomas (Table 1). Other histological subtypes represented 21.8% of the cases (data not shown). Mean age at cohort entrance was 51.6 years and a mean age at lung cancer diagnosis was 64.4 years. At baseline, 43.2% of the women reported a PA level of 5-6 and in total nearly 74.0 % reported a PA level of 5 or higher. Fifty-nine participants (7.5%) later identified with lung cancer were never smokers at baseline, whereas 597 (76.3%) were current smokers. Women with a PA level of 5 or higher were more frequently never smokers, had a lower BMI, and a higher fruit and vegetable consumption than their counterparts with lower PA levels (Table 1).

PA level at baseline was negatively associated with risk of lung cancer overall (*P for trend*=0.000). Participants with a PA level of 1-2 had a 49% higher risk of lung cancer overall compared to those with PA levels of 5-6 (HR=1.49; 95% CI 1.15-1.93). This association was stronger in repeated measurement analyses (HR=2.01; 95% CI 1.39-2.91) and a similar trend was observed (*P for trend*=0.000). Participants with a PA level higher than 5-6 showed a tendency for a reduced risk of lung cancer overall (HR for PA level 7-8=0.82; 95% CI 0.67-1.01 and HR for PA level 9-10=0.95; 95% CI 0.69-1.32), which did not change substantially in repeated

measurement analyses. The results for adenocarcinoma showed a comparable statistically significant trend; but no statistically significant associations were found for any of the other investigated histological subtypes (Table 2).

Interactions between PA and categories of BMI, smoking status, and years of education were not significant (*P for trend*=0.87, *P for trend*=0.42, and *P for trend*=0.24, respectively). In spite of this, we investigated the association between PA and risk of lung cancer overall in analyses stratified by smoking status and BMI. Analyses stratified by smoking status at baseline showed no association with lung cancer overall in never and former smokers. However, for current smokers with PA levels 1-2 there was a statistically significant, increased risk of lung cancer overall (HR=1.50, 95% CI 1.13-2.00), with a consistent decreasing risk with increasing PA levels (Table 3). Repeated measurement analyses yielded similar results for never smokers, but the association among former and current smokers with PA levels 1-2 was significantly stronger (HR=3.56, 95% CI 1.64-7.76 and HR=1.73, 95% CI 1.13-2.65, respectively) (Table 3).

Analyses stratified by BMI at baseline showed a higher risk of lung cancer overall among normal-weight participants with lower PA levels (77% for PA levels 1-2 and 32% for PA levels 3-4) (Table 3). No significant associations were found for overweight or obese participants. The repeated measurement analyses showed similar results for normal-weight women, but there was a significant, reduced risk in overweight participants with increasing PA levels (Table 3).

Results of multiple imputation analyses did not suggest that missing information influenced the associations between PA level and lung cancer overall or between PA level and the investigated subtypes of lung cancer. However, the associations were slightly stronger for lung cancer overall and for adenocarcinoma (Table 4). The model stratified for smoking status yielded results comparable to those of the baseline analyses. Stratification for BMI yielded results similar to those of baseline analyses for normal weight and overweight participants, but we found a significant, increased risk of lung cancer in obese participants.

Discussion

In this large Norwegian cohort, we found an inverse dose-response association between self-reported PA level and risk of lung cancer overall. The results were consistent when using baseline data alone and when using repeated measurements of PA, BMI and smoking status. We observed a similar trend for adenocarcinomas; however no statistically significant associations were found for squamous cell carcinoma or small cell carcinoma. Our findings further suggest a more pronounced association between lung cancer and PA levels in current smokers, with an increased risk of 50% for the lowest PA levels and a 20% decreased risk for higher levels of PA, but no significant associations were found in never and former smokers at baseline. However, repeated measurement analyses revealed a significant inverse association only in former smokers, not never smokers. In baseline analyses, we found a reduced risk of lung cancer in normal-weight participants with increasing PA. We also found a reduced risk among overweight participants in repeated measurement analyses, but we found no associations among participants with obesity.

The heterogeneity between studies on the relationship between lung cancer and PA level is challenging, as the type of PA measured, the lack of dose-response data, study design, sex, and sample size make it difficult to compare these studies and to calculate overall estimates. Most studies that investigated the association between PA and the risk of lung cancer in women focused on recreational PA [9, 10, 28]; fewer studies have captured total PA (including recreational, occupational, household, and transportation) [29, 15, 30, 12, 31]. In its Second Expert Report from 2007, the WCRF/AICR concluded that the evidence for an association between PA and lung cancer is “limited-suggestive” [5]. The five cohort studies included in that comprehensive report all had overall summaries of PA (recreational and non-recreational), but the lack of detail in the evidence made dose-response analyses impossible, and only two of the studies included women [5]. The NIH-AARP Diet and Health Study by Leitzmann and colleagues found an inverse association between total PA (both recreational and non-recreational) and risk of lung cancer in analyses adjusted for sex, and these findings were consistent in sex-specific analyses and over other covariates, i.e., age, education level, and BMI [15]. Our results showed a significant decreased risk of lung cancer, and thus are similar to those of the NIH-AARP Diet and Health Study; however the measurements of PA between the studies are not comparable [15]. The results of the two most recent meta-analyses on recreational PA and risk of lung cancer showed statistically significant, inverse associations in the range of 13%-25% for lung cancer from cohort studies [9, 10]; however these estimates included several studies that enrolled only men. One meta-analysis that estimated the association among women separately found an overall relative risk of 0.73 (95% CI 0.63-0.86); however it included both case-control and cohort studies, and

the heterogeneity between the studies was found to be high (I-squared=50.9%) [9]. Based on cohort studies that included sex-adjusted analysis and/or specific analysis of women, five found inverse associations [14, 32, 15, 33, 34], while 12 others [35, 30, 36-39, 31, 29, 12, 16, 40, 41, 28] found no associations between the risk of lung cancer and PA level (including both recreational and non-recreational PA).

The investigation of the association between PA and lung cancer is complicated by tobacco smoking, which acts as a powerful confounder in the causation of lung cancer, and the protective effect of PA observed among smokers may be confounded by cigarette smoking [42]. The solution to this problem may be to investigate this association among never smokers only [16]. However, that could represent a selected group bias, with participants who have a low prevalence of other exposures of relevance [43]. A recent meta-analyses stratified by smoking behavior to address this potential bias, and concluded that PA was not related to lung cancer in never smokers and that there was a reduced risk in former and current smokers [42]. Our stratified, repeated measurement analyses indicated that the risk of lung cancer was reduced among current and former smokers with increasing PA levels. We found no association between lung cancer and PA level in never smokers. These results are consistent with findings from other studies [42, 30, 44, 14-16]. However, the relatively low number of lung cancer cases among never smokers made these analyses less robust, and must therefore be interpreted with caution.

The reduced risk of lung cancer was more profound among normal-weight and overweight women with increasing PA levels in our study. This corresponds with findings from other studies [44, 33, 32, 15], which showed that low and medium BMI reduced the risk of lung cancer, as other cohort studies adjusted for BMI and did not report separate their analyses [14, 30, 31, 40, 16, 12, 29].

The strengths of our study include its prospective, population-based design and the use of a high-quality, national cancer registry to identify lung cancer cases [17]. The presence of repeated measurements on the exposure and potential confounders is also a considerable strength. The prospective design precluded bias attributable to recall bias of PA by participants independently of lung cancer. Moreover, the PA scale we used has been validated [19] and correlated well with all-cause mortality rates [45]. Our assessment of PA in the NOWAC Study compromised total PA, covering the domains of recreation, occupation, household and transportation, with one repeated measurement during follow-up. Multiple imputation of missing data, in addition to baseline analyses, confirmed our results. Our large prospective study included a high number of lung cancer cases, and thus it was possible to investigate histological subtypes. Finally, the study is based on a relatively long follow-up (13 years).

The total self-reported measure of PA in the NOWAC Study cannot differentiate intensity, duration, and frequency of PA, nor the type of PA, and given the self-reported nature of this variable, measurement errors cannot be ruled out. However, measurement errors would likely lead to a non-differential bias and a potential underestimation of the true effect. The PA assessment used in this study may not apply to women in other countries. Moreover, the potential for residual confounding, in particular by smoking habits, is a possible explanation, as the protective association we observed was seen only among smokers. Certain other lifestyle-related factors may act as confounders or effect-modifiers and cannot be excluded.

Conclusions

In this large cohort study we found an inverse dose-response relationship between PA level and risk of lung cancer overall and between PA level and adenocarcinoma among women. Our results were consistent when using baseline data and repeated measurements of PA level, with adjustments for repeated measurements of smoking status and BMI. Women who were within the normal and overweight range appeared to benefit from a higher protective effect of PA, as did those who were current and former smokers. No associations between PA and lung cancer were found among never smokers.

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Compliance with Ethical Standards:

Conflict of interest: The authors declare that they have no conflict of interest.

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

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Table 1. Selected participant characteristics at study enrollment (baseline) in the Norwegian Women and Cancer study by physical activity (PA) level (n=80,802)

Characteristic	PA level					
	1-2 N=3,730 (4.6%)	**3-4 N=17,684 (21.9%)**	**5-6 N= 3,863 (43.2%)**	**7-8 N= 20,435 (25.3%)**	**9-10 N=4,090 (5.1%)**	**Total**
Age (mean, ±SE)	53.0 (0.1)	52.0 (0.05)	51.4 (0.03)	51.1 (0.04)	51.7 (0.10)	51.6 (0.02)
Follow-up time years (mean, ±SE)	12.8 (0.07)	13.1 (0.03)	13.0 (0.02)	12.7 (0.03)	12.8 (0.06)	12.9 (0.01)
Lung cancer overall n (%)	73	215	314	138	42	782 (100%)
Adenocarcinoma[1]	25	106	140	63	19	353 (45.1%)
Squamous cell carcinoma[1]	11	26	50	18	7	112 (14.3%)
Small cell carcinoma[1]	18	35	54	30	9	146 (18.7%)
BMI (mean, ±SE) [2]	26.9 (0.09)	25.8 (0.03)	24.6 (0.02)	23.8 (0.02)	23.6 (0.05)	24.7 (0.01)
Years of education (mean, ±SE)[3]	11.4 (0.06)	12.1 (0.03)	12.3 (0.02)	12.6 (0.02)	11.8 (0.06)	12.3 (0.019
Smoking status (%)[4]						
Never	29.5	36.1	37.2	37.3	35.3	37.1
Former	29.7	31.2	32.8	35.0	33.0	33.3
Current	39.4	31.4	28.9	26.3	30.2	29.6
Pack years of smoking in ever smokers (mean, ±SE)	13.7 (0.21)	11.4 (0.09)	10.0 (0.06)	9.4 (0.07)	9.6 (0.17)	10.3 (0.04)
Alcohol consumption, mean ±SE (g/day)[5]	3.7 (0.11)	3.7 (0.04)	3.5 (0.03)	3.7 (0.04)	3.5 (0.10)	3.6 (0.02)
Fruit consumption, mean ±SE (g/day)	1.2 (0.02)	1.4 (0.01)	1.5 (0.01)	1.65 (0.01)	1.7 (0.02)	1.5 (0.00)
Vegetable consumption, mean ±SE (g/day)	121.1 (1.5)	131.5 (0.64)	140.6 (0.47)	155.1 (0.67)	166.7 (1.8)	142.7 (0.32)

SE: standard error; BMI: body mass index.
[1]Histological subtypes of lung cancer: only the main subtypes are included.
[2]Number of total missing in BMI 782 (1.0%)
[3]Number of total missing in years of education 4,327 (5.4%)
[4]Number of total missing in smoking status 1,151 (1.4%)
[5]Number of total missing in alcohol consumption 2,095 (2.6%)

Table 2. Multivariable hazard ratios and 95% confidence intervals of lung cancer risk by physical activity (PA) level in baseline analyses (n=80,802) and repeated measurement analyses (n=54,691) in the Norwegian Women and Cancer Study

		Number of lung cancer cases	PA level					
			1- 2	3-4	(ref)	7-8	9-10	P trend
Baseline analyses[1]	Lung cancer overall	782	1.49 (1.15-1.93)	1.21 (1.01-1.44)	1.00	0.82 (0.67-1.01)	0.95 (0.69-1.32)	0.000
	Adenocarcinoma	353	1.27 (0.82-1.95)	1.39 (1.08-1.80)	1.00	0.81 (0.60-1.10)	0.97 (0.60-1.56)	0.002
	Squamous cell carcinoma	112	1.29 (0.66-2.51)	0.89 (0.55-1.44)	1.00	0.68 (0.40-1.17)	0.95 (0.43-2.11)	0.162
	Small cell carcinoma	146	1.91 (1.11-3.30)	1.10 (0.72-1.69)	1.00	1.10 (0.70-1.72)	1.20 (0.59-2.45)	0.467
Repeated measurement analyses[2]	Lung cancer overall	368	2.01 (1.39-2.91)	1.42 (1.09-1.83)	1.00	0.91 (0.69-1.21)	0.91 (0.55-1.51)	0.000
	Adenocarcinoma	163	1.78 (0.97-3.28)	1.67 (1.14-2.45)	1.00	0.97 (0.63-1.47)	0.71 (0.31-1.66)	0.002
	Squamous cell carcinoma	49	1.67 (0.62-4.55)	1.13 (0.56-2.28)	1.00	0.71 (0.31-1.61)	1.18 (0.35-3.99)	0.27
	Small cell carcinoma	72	2.15 (1.02-4.51)	1.06 (0.57-1.95)	1.00	0.90 (0.46-1.74)	1.33 (0.51-3.47)	0.24

[1]Multivariable model adjusted for body mass index, years of education, smoking habits (status and pack year), and fruit consumption (g/day). Model stratification by birth cohort (strata 1: enrolled in 1991-92 and born 1943-57; strata 2: enrolled in 1996-97 and born 1927-42; strata 3: enrolled in 1996-97 and born 1943-57; and strata 4: enrolled in 2003-07 and born 1943-57).

[2]Repeated measurement of PA (with additional follow-up information on body mass index, smoking status, and fruit consumption), time varying.

Table 3. Multivariable hazard ratios and 95% confidence intervals of the association between physical activity (PA) level and risk of lung cancer overall by smoking status and body mass index (BMI) in baseline analyses (n=80,802) and repeated measurement analyses (n=54,691) in the Norwegian Women and Cancer Study

		PA levels				
Baseline analyses	**Number of lung cancer cases**	**1-2**	**3-4**	**5-6**	**7- 10**	**P trend**
Smoking status	Never (n=59)	1.19 (0.36-3.97)	0.99 (0.52-1.90)	1.00	0.87 (0.46-1.65)	0.642
	Former (n=126)	1.50 (0.70-3.22)	1.54 (0.99-2.39)	1.00	1.08 (0.69-1.68)	0.132
	Current (n=597)	1.50 (1.13-2.00)	1.17 (0.96-1.43)	1.00	0.80 (0.65-0.99)	0.000
BMI	Normal (n=541)	1.77 (1.29-2.44)	1.32 (1.06-1.63)	1.00	0.82 (0.66-1.02)	0.000
	Overweight (n=184)	1.10 (0.63-1.93)	1.03 (0.73-1.46)	1.00	0.99 (0.68-1.46)	0.874
	Obese (n=57)	0.99 (0.46-2.14)	0.96 (0.52-1.79)	1.00	0.78 (0.33-1.84)	0.554
Repeated measurement analyses[1]						
Smoking status	Never (n=20)	1.85 (0.22-15.35)	1.46 (0.46-4.64)	1.00	1.41 (0.49-4.06)	0.88
	Former (n=91)	3.56 (1.64-7.76)	2.21 (1.28-3.82)	1.00	1.44 (0.84-2.46)	0.015
	Current (n=257)	1.73 (1.13-2.65)	1.22 (0.90-1.66)	1.00	0.75 (0.54-1.04)	0.000
BMI	Normal (n=249)	1.94 (1.21-3.11)	1.34 (0.97-1.85)	1.00	0.90 (0.66-1.23)	0.001
	Overweight (n=91)	2.43 (1.21-4.88)	1.50 (0.91-2.47)	1.00	1.01 (0.57-1.81)	0.016
	Obese (n=28)	1.59 (0.51-4.93)	1.73 (0.71-4.18)	1.00	0.58 (0.12-2.73)	0.111

[1]Model 1: Stratified multivariable model adjusted for BMI (when stratified according smoking status), years of education (0-9; 10-12; 13+), smoking status (never, former, current, when stratified according BMI), quintiles of fruit consumption (g/day). Model stratification by birth cohort (strata 1: enrolled in 1991-92 and born 1943-57; strata 2: enrolled in 1996-97 and born 1927-42; strata 3: enrolled in 1996-97 and born 1943-57; and strata 4: enrolled in 2003-07 and born 1943-57).

Table 4. Multivariable hazard ratios and 95% confidence intervals in *chained multiple imputation* analyses of the association between physical activity (PA) and lung cancer including baseline and repeated measurements in the Norwegian Women and Cancer Study (n=80,802)

		PA levels					
	Number of lung cancer cases	1-2	3-4	5-6	7-8	9-10	P trend
Lung cancer overall	866	1.73 (1.30-2.30)	1.33 (1.08-1.64)	1.00	0.84 (0.67-1.06)	0.87 (0.57-1.32)	0.000
Adenocarcinoma	382	1.50 (0.94-2.39)	1.42 (1.06-1.90)	1.00	0.85 (0.61-1.19)	0.60 (0.27-1.31)	0.001
Squamous carcinomas	125	1.48 (0.71-3.11)	1.29 (0.78-2.14)	1.00	0.88 (0.47-1.66)	1.06 (0.38-2.95)	0.163
Small cell	165	1.82 (1.01-3.29)	0.93 (0.57-1.52)	1.00	0.80 (0.48-1.35)	1.16 (0.53-2.52)	0.156
Lung cancer overall stratified analyses by		1-2	3-4	5-6	7-8	9-10	
Smoking	Never n=61	1.39 (0.41-4.71)	1.23 (0.63-2.42)	1.00	1.26 (0.66-2.40)	0.45 (0.06-3.34)	0.600
	Former n=140	2.34 (1.42-3.85)	1.63 (1.16-2.31)	1.00	0.96 (0.65-1.41)	1.08 (0.55-2.11)	0.000
	Current n=665	1.74 (1.29-2.33)	1.29 (1.04-1.59)	1.00	0.79 (0.61-1.01)	0.89 (0.57-1.38)	0.000
		1-2	3-4	5-6	7-10		
Body mass index	Normal n=608	1.60 (1.12-2.28)	1.39 (1.12-1.73)	1.00	0.84 (0.67-1.05)		0.000
	Overweight n=196	2.37 (1.54-3.63)	1.32 (0.95-1.83)	1.00	1.03 (0.71-1.50)		0.001
	Obese n=62	1.94 (0.98-3.84)	1.38 (0.75-2.52)	1.00	0.66 (0.26-1.69)		0.012

[1]Model 1: Multivariable model adjusted for body mass index, years of education, smoking status (never former current), fruit consumption (g/day). Model stratification by birth cohort (strata1: enrolled in 1991-92 and born 1943-57; strata 2: enrolled in 1996-97 and born 1927-42; strata 3: enrolled in 1996-97 and born 1943-57; and strata 4: enrolled in 2003-07 and born 1943-57).

Note: Multiple imputation of covariates in the multivariable analyses conducted with chained equation. 20 imputed data sets were generated.

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Author name KRISTIN BENJAMINSEN BORCH

Are you the corresponding author? ☒ Yes ☐ No

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