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Air pollution, physical activity and ischemic heart disease - A prospective cohort study of interaction effects

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Air pollution, physical activity and ischemic heart disease - A prospective cohort study of interaction effects

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31 Abstract

32 **Objective:** To assess a possible interaction effect between physical activity and air pollution on first
33 incidence of ischemic heart disease (IHD).

34 **Design:** Prospective cohort study

35 **Setting:** Umeå, Northern Sweden

36 **Participants:** We studied 34,748 adult participants of Västerbotten Intervention Programme cohort
37 from 1990 to January 2014. Annual particulate matter concentrations ($PM_{2.5}$ and PM_{10}) at the
38 participants' residential addresses were modelled and a questionnaire on frequency of exercise and
39 active commuting was completed at baseline. Cox proportional hazards modelling was used to estimate
40 1) association with physical activity at different levels of air pollution, and 2) the association with
41 particulate matter at different levels of physical activity.

42 **Outcome:** First incidence of IHD.

43 **Results:** Over a mean follow-up of 12.4 years, there were 1,148 IHD cases. Overall, we observed an
44 increased risk of IHD among physically active individuals with higher concentrations of particles at their
45 home address. Exercise at least twice a week was associated with a lower risk of IHD among participants
46 with high residential $PM_{2.5}$ (0.60; 95% CI: 0.44-0.82) and PM_{10} (0.55; 95% CI: 0.4-0.76). The same
47 beneficial effect was not observed with low residential $PM_{2.5}$ (0.94; 95% CI: 0.72-1.22) and PM_{10} (0.99;
48 95% CI: 0.76-1.29). An increased risk associated with higher long-term exposure to particles was only
49 observed among participants never exercising in training clothes and among those not performing any
50 active commuting. However, only the interaction effect on hazard ratios for exercise was statistically
51 significant.

52 **Conclusion:** Exercise was associated with a lower risk of first incidence of IHD among individuals with
53 higher residential particle concentrations. An air pollution-associated risk was only observed among
54 those who exercised less. The findings support the promotion of physical activity and a mitigation of air
55 pollution.

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57 **Key Words:** Air pollution, $PM_{2.5}$, PM_{10} , exercise, interaction, ischemic heart disease

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Strengths and limitations of this study

- This study simultaneously evaluated the impact of physical activity and air pollution and their interaction on first incident IHD cases in a population with relatively low level of air pollution concentrations.
- For air pollution exposure, this study used individual time varying exposures of annual mean concentrations during follow-up based on population address registries.
- Another strength is the prospective design and the availability of baseline data on several important confounders.
- No exposure-response assessment could be performed since the statistical power only allowed for the formation of two exposure categories.
- Differences in air pollution exposure during active commuting might cause possible bias estimates due to exposure misclassification.

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1 Introduction

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109 Cardiovascular disease (CVD) is the most important cause of morbidity and premature mortality
110 worldwide, accounting for 422.3 million cases and 17.92 million deaths in 2015 [1]. There is solid
111 evidence that inflammation is a key upstream pathogenic mechanism [2]. Ambient air pollution,
112 generally comprising ozone, sulphur dioxide, nitrogen dioxide and particulate matter (PM), is a leading
113 contributor to the global burden of disease and an important risk factor for morbidity and mortality.
114 Particulate matter is often measured as PM_{2.5}, to represent particles with a diameter of 2.5 micrometres
115 or less, and PM₁₀, to represent particles with a diameter of 10 micrometres or less. Ambient PM_{2.5}
116 exposure alone has been estimated to account for 4.2 million deaths in 2015, of which 1.5 million deaths
117 were caused by ischemic heart diseases (IHD) [3]. The underlying mechanisms mediating the pathogenic
118 impact of air pollution involve systemic oxidative stress and inflammation [4,5]. Physical activity is a
119 salutogenic factor in numerous non-communicable chronic diseases (NCDs), with physical inactivity
120 being responsible for 6% of the burden of disease from coronary heart disease [6,7]. The beneficial
121 effects of physical activity include protection against low-grade inflammation by releasing anti-
122 inflammatory substances, such as interleukin 6, from contracting muscles [8,9].

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124 Rapid urbanization and increased use of motorized transport contribute to modern day problems such
125 as traffic congestion, traffic related air pollution and lack of physical activity. Promotion of active
126 transportation by changing mode of transport from car to cycling and walking are among the different
127 strategies used to tackle these challenges [10–12]. As inflammation is a causative mechanism for
128 cardiovascular disease, it is conceivable that the anti-inflammatory effects of physical activity may
129 mitigate the harmful effects associated with exposure to air pollution. However, one major concern with
130 physical activity in a polluted environment is the increased inhalation of particles due to an increase in
131 respiratory volume that may counteract the beneficial effects of physical activity [13,14].

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133 The long-term effects of air pollution among individuals with different levels of leisure time physical
134 activity have been estimated within the Danish Diet, Cancer, and Health cohort. The incidence of
135 diabetes was assessed in relation to leisure time physical activity and nitrogen dioxide (NO₂)
136 concentration at the home address. Residential NO₂ was found to be associated with increased
137 incidence of diabetes, but only among physically active individuals [15]. As far as we know, only one
138 study has examined the modifying effect of air pollution on the association between physical activity
139 and cardiovascular disease. In their recent study, Kubesch and colleagues conclude that physical activity
140 reduced the risk of first incidence of myocardial infarction (MI) and recurrent MI among individuals with
141 high NO₂ concentration at the residential addresses [16]. As only one pollutant (NO₂) and only one
142 cardiovascular outcome (MI) have been studied, the knowledge of a possible interaction between air
143 pollution and physical activity on CVD is inconclusive.

144 A Taiwanese study found an independent inverse association of habitual physical activity with
145 inflammation across different levels of PM_{2.5} exposure, although long term exposure was associated
146 with increased inflammation at all levels of physical activity [17].

147 We therefore aimed to examine interaction effects between physical activity and long-term exposure to
148 PM_{2.5} and PM₁₀ at residential addresses on the incidence of ischemic heart disease (IHD). We wanted to

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3 149 assess: 1) whether air pollution modifies the beneficial effects of physical activity on IHD, and 2)
4 150 whether physical activity modifies the harmful effects of air pollution on IHD.

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10 154 2 Methods

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13 156 To determine the interaction effect between air pollution and physical activity on IHD incidence, we
14 157 combined cohort data which comprised risk factors for IHD, national registry data on IHD incidence from
15 158 the Swedish National Board of Health and Welfare, and yearly annual mean air pollution particle
16 159 concentrations at the individuals' residential addresses using dispersion models from the Swedish Clean
17 160 Air and Climate Research Program (SCAC).

19 161

20 162 VIP (Västerbotten Intervention Programme) is a population based screening and prospective cohort
21 163 study, developed to reduce the risk of future CVD and diabetes by promoting a healthy lifestyle among
22 164 individuals living in the Västerbotten region. The SCAC developed methods to estimate exposure to
23 165 source-specific particulate matter such as PM_{2.5} and PM₁₀ and at residential addresses in Gothenburg,
24 166 Stockholm and Umeå.

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27 168 2.1 Study population

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29 170 VIP is an ongoing population-based health investigation survey of all individuals at ages 40, 50 or 60
30 171 years, depending upon risk factors, living in the Västerbotten region, who are invited to participate in
31 172 systematic risk factor screening and individual counselling about healthy lifestyle habits. A detailed
32 173 description of VIP has been presented elsewhere [18]. Between 1990 and 2014, a total of 42,488 of the
33 174 VIP participants that lived in Umeå Municipality during the study period were included in the analysis.
34 175 After exclusion of 7,740 participants with missing information on exercise, the study sample thus
35 176 consisted of 34,748 individuals, 53% men and 47% women, 40-60 years of age at baseline examination,
36 177 with no previous history of IHD at time of enrolment. After exclusion of individuals with missing
37 178 information on included confounders the final number of included individuals were 31424 and 29218 for
38 179 the analyses of exercise in training clothes and active commuting, respectively. All participants in the VIP
39 180 gave their informed written consent, and the study was approved by the Regional Ethics Review Board
40 181 at Umea University (DNR: 2014-136-32M and 2015/16-31Ö).

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44 183 2.2 Leisure time exercise and active commuting

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46 185 The VIP questionnaire includes various self-reported information on physical activity including frequency
47 186 of leisure time physical activity and active commuting (cycling or walking to and from work). The
48 187 association with IHD was assessed in relation to frequency of exercise in training clothes and amounts of
49 188 active commuting. Exercise during the previous three months was categorized as never, rarely, once per
50 189 week, 2-3 times per week or more than 3 times per week. Based on this information, participants were
51 190 categorized as "Twice per week or more" if they exercised with a frequency of 2-3 times per week and
52 191 more, "At most once a week" if they exercised rarely or once per week, and "Never" if no activity was
53 192 performed. For active commuting, participants were asked about their mode of transport to work each
54 193 season. Participants were classified in three categories: "Non- active commuting" if commuting every

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194 season by car or bus, “At most two seasons out of four” if cycling or walking at most half a year and
195 “More than two seasons out of four”, if cycling and walking more than half a year.

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199 2.3 Covariates

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201 The VIP questionnaire also gathered information on participants’ educational status, occupation,
202 smoking, alcohol intake and economic status. Education was defined according to the International
203 Standard Classification of Education (ISCED), United Nations Educational, Scientific and Cultural
204 Organization (UNESCO) 1997. Participants were asked about the highest level education they had
205 achieved with eight predefined categories ranging from “pre-school” to “university education.” Alcohol
206 intake was assessed by the reported frequency of consumption with answering options that ranged
207 from “Never” to “2-4 times/week.” Information on smoking was gathered by using the question, “How
208 often do you smoke?” Information on occupational status was obtained with a question, “What kind of
209 job do you have nowadays?” with the answering options of eight predefined categories. Finally,
210 information on occupation status was asked with the question, “What is your current occupation?” with
211 8 categories ranging from permanently employed to retired.

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213 2.4 Air pollution concentrations

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216 Annual mean total concentrations of PM_{2.5} and PM₁₀ for the years 1990-2011 (and thereafter linearly
217 extrapolated up until year 2014) were obtained from the SCAC research program, described in detail
218 elsewhere [19]. Briefly, concentrations of PM_{2.5} and PM₁₀ were estimated within SCAC by applying
219 dispersion models on local or regional emission inventories. These emission inventories contain detailed
220 information on emissions from different source categories, such as road traffic exhaust, road traffic non-
221 exhaust, domestic heating, shipping and industrial activities. For Umeå, inventories were validated
222 through monitoring for consistency. Emissions from small-scale residential heating were assessed using
223 registry data from chimney sweepers that included the type of wood stove or boiler. The addresses of
224 these residences were geocoded using the geographical centre coordinate of the estate. Road traffic
225 emission factors for PM exhaust for different vehicle types, speeds and driving conditions were
226 calculated based on the Handbook Emission Factors for Road Transport (HBEFA) version 3.1 [20].
227 Estimates for non-exhaust contribution from brake and tire wear were based on Omstedt et al. [21]. The
228 annual average emission from shipping was used in the modelling on a 1x1 km² grid resolution. The
229 emissions from other sources such as industrial processes, off-road machinery and agriculture was
230 collected from Swedish Meteorological and Hydrological Institute (SMHI). To obtain annual average
231 emissions of PM_{2.5} and PM₁₀, Gaussian models included in the Airviro air quality management system
232 (SMHI, 2010) were used for simulation based on hourly meteorological data for 1990, 2000 and 2011
233 [22]. The comparison between measured and modelled PM_{2.5} and PM₁₀ agreed well at most monitoring
234 stations ($r^2=0.87$ and $r^2=0.65$, respectively).

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236 2.5 Outcome

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237 We linked the records in VIP and through the unique Swedish personal identification number with data
238 on first IHD event cases from the National Patient Register and the Cause of Death Register, both at the
239 National Board of Health and Welfare, using primary discharge diagnoses for IHD according to
240 International Classification of Diseases, 10th revision (ICD-10): code I20-125.

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243 2.6 Participants and public involvement

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245 There was no participants and public involvement in conducting or reporting our research.

246 2.7 Statistical Analysis

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248 We performed survival analyses using Cox regression with age as underlying time scale to estimate
249 hazard ratios (HRs), and 95% confidence intervals (CIs), to estimate 1) the association between first
250 incident IHD and air pollution exposure at different levels of physical activity and 2) the association
251 between first incident IHD and physical activity at different levels of air pollution exposure. Follow-up
252 started at date of recruitment to the cohort and ended with the earliest of the date of first IHD case,
253 emigration, death, or 31 December 2013. Interaction between physical activity and air pollution and
254 their impact on IHD was studied by introducing an interaction term into the model. Residential annual
255 mean particle concentrations were categorized as below or above the median concentration for PM_{2.5}
256 and PM₁₀, respectively. Interaction with physical activity was assessed based on 1) the frequency of
257 exercise in training clothes and 2) the number of seasons the individual walked or cycled to work. Active
258 commuting by walking or cycling was categorized into three groups: non-active commuters, active
259 commuters at most half of the year (up to two out of four seasons), active commuters more than half a
260 year (more than two out of four seasons). Estimates were adjusted for: calendar year as a penalized
261 cubic spline with 3 degrees of freedom, gender (male vs female), highest education level (compulsory,
262 high school, university), alcohol intake (never, once/month or sometimes, 2-4 times/month, 2-3
263 times/week, ≥4 times/week), smoking (previous non-regular smoker, non-regular smoker, cigarette
264 smoker, cigar or pipe smoker), occupation (gainfully employed, unemployed, not gainfully employed,
265 retired), and registry data on area level mean income. In the basic model we adjusted only for gender
266 and exposure year. All analyses were performed using R version 3.4.2, and the statistical inference was
267 conducted with a 5% significance level.

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269 3 Results

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271 The mean age at recruitment to this cohort was 45.8 years. Among the 34,748 participants 1,148 cases
272 of IHD were identified during a mean follow-up time of 12.4 years. Table 1 summarizes characteristics of
273 participants according to different levels of leisure time physical activity. Participants not reporting any
274 leisure time exercise were older and more likely to be male, non-commuters and to belong to a lower
275 socioeconomic group. Subjects performing moderate to high-level physical activity, were more likely to
276 be women, non-smokers, and active commuters. The 5-year mean of PM₁₀ and PM_{2.5} concentration
277 were different between leisure time physical activity categories, with at most 7 and 6% difference
278 respectively for PM₁₀ and PM_{2.5}.

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Table 1: Characteristics of participants at different levels of exercise in training clothes at baseline

Characteristics	Never	At most once a week	Twice per week or more	p
Exercise in training clothes n (%)	13043 (37.5)	14994 (43.2)	6711 (19.3)	
PM ₁₀ , µg/m ³ (mean (SD))	10.93 (2.00)	11.06 (1.96)	10.39 (1.94)	<0.001
PM _{2.5} , µg/m ³ (mean (SD))	6.41 (1.12)	6.49 (1.12)	6.11 (1.11)	<0.001
Frequency of active commuting (%)				<0.001
Non-active commuting	6369 (48.8)	6409 (42.7)	2666 (39.7)	
At most two seasons of four	1806 (13.8)	2547 (17.0)	1037 (15.5)	
More than two seasons of four	3506 (26.9)	4976 (33.2)	2555 (38.1)	
Missing	1362 (10.4)	1062 (7.1)	453 (6.8)	
Alcohol intake (%)				<0.001
Never	135 (1.0)	120 (0.8)	79 (1.2)	
Once/month or sometimes	5337 (40.9)	5950 (39.7)	2790 (41.6)	
2-4 times/month	2000 (15.3)	2436 (16.2)	1061 (15.8)	
2-3 times/week	97 (0.7)	93 (0.6)	54 (0.8)	
≥ 4 times/week	5068 (38.9)	5861 (39.1)	2265 (33.8)	
Missing	406 (3.1)	534 (3.6)	462 (6.9)	
Smoking (%)				<0.001
Never smoker	5139 (39.4)	7240 (48.3)	3467 (51.7)	
Previous non-regular smoker	1072 (8.2)	1458 (9.7)	711 (10.6)	
Non-regular smoker	581 (4.5)	807 (5.4)	348 (5.2)	
Previous regular smoker	2729 (20.9)	2865 (19.1)	1201 (17.9)	
Cigarette smoker	2789 (21.4)	1805 (12.0)	426 (6.3)	
Cigar or pipe smoker	186 (1.4)	130 (0.9)	45 (0.7)	
Missing	547 (4.2)	689 (4.6)	513 (7.6)	
Highest education level (%)				<0.001
Compulsory	5534 (42.4)	4319 (28.8)	1369 (20.4)	
High	3573 (27.4)	4116 (27.5)	1951 (29.1)	
University	3449 (26.4)	5933 (39.6)	2911 (43.4)	
Missing	487 (3.7)	626 (4.2)	480 (7.2)	
Gender %, (men)	7072 (54.2)	8036 (53.6)	3274 (48.8)	<0.001
Age, y (mean (SD))	47.28 (9.09)	45.27 (9.02)	44.32 (8.61)	<0.001
Occupation (%)	<0.001			
Gainfully employed	10536 (80.8)	12690 (84.6)	5452 (81.2)	
Unemployed	478 (3.7)	382 (2.5)	174 (2.6)	

Characteristics	Never	At most once a week	Twice per week or more	p
Not gainfully employed	318 (2.4)	352 (2.3)	160 (2.4)	
Retired	673 (5.2)	449 (3.0)	194 (2.9)	
Missing	1038 (8.0)	1121 (7.5)	731 (10.9)	
Mean income for the neighbourhood (SEK)	128285.70 (23017.70)	130332.22 (23875.04)	130221.55 (24605.92)	<0.001

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298 Compared with individuals who reported no exercise, those participants that exercised at least twice per
299 week had a 24% lower risk of IHD (Table 2). The corresponding overall estimate associated with active
300 commuting was a 13% reduced risk of IHD among individuals commuting more than two seasons per
301 year.

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302 Allowing for an interaction between the frequency of exercise in training clothes and particle
303 concentrations (PM₁₀ and PM_{2.5}) at the home address, the average 24% risk reduction from exercising at
304 least twice per week was found to be driven by an interaction between exercise and particle exposure
305 with 45% and 40% risk reduction among individuals with high PM₁₀ and PM_{2.5} concentrations,
306 respectively (table 2). The interaction coefficients estimating the additional benefit of exercise among
307 individuals with a high exposure to particles at their home address were a 3% increased and a 44%
308 reduced risk among those with high PM₁₀ concentrations and 0% and 36% risk reductions among those
309 with high PM_{2.5} concentrations.

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310 For active commuters with low particle exposure at their home address, the risk of incident IHD was 17%
311 and 18% higher among those commuting one or two seasons per year and 7% and 3% lower among
312 those commuting at least two seasons per year, for PM₁₀ and PM_{2.5} respectively. The benefit of active
313 commuting was larger among individuals with a high particle concentration at their home address: risk
314 reductions for active commuting during one or two seasons were 12% and 13% and for more than two
315 seasons 18% and 21% respectively, compared with non-active commuters. No statistically significant
316 interaction was found between active commuting and particle concentrations at the home address.

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Table 2: Hazard ratios (95% CI) for IHD associated with different exercise and commuting habits among persons with different air pollution exposure at home addresses.

Exercise in training clothes	Overall model with no interaction effects	Adjusted ^a HRs in categories of high and low particle exposure		Adjusted ^a interaction hazard ratio
		Low PM ₁₀ ^b	High PM ₁₀ ^b	
Never	1	1	1	
≤ once/week	1.03 (0.90-1.16)	1.01 (0.84-1.21)	1.04 (0.88-1.23)	1.03 (0.81-1.32)
≥ twice/week	0.76 (0.62-0.93)	0.99 (0.76-1.29)	0.55 (0.40-0.76)	0.56 (0.37-0.84)
		Low PM _{2.5} ^c	High PM _{2.5} ^c	
Never		1	1	
≤ once/week		1.03 (0.86-1.23)	1.03 (0.87-1.22)	1.00 (0.78-1.28)
≥ twice/week		0.94 (0.72-1.22)	0.60 (0.44-0.82)	0.64 (0.43-0.96)
Active commuting per season		Low PM ₁₀ ^b	High PM ₁₀ ^b	
Non-active commuting	1	1	1	
≤ two season of four	1.01 (0.86-1.19)	1.17 (0.93-1.47)	0.88 (0.70-1.11)	0.76 (0.55-1.04)
> two seasons of four	0.87 (0.76-0.998)	0.93 (0.76-1.14)	0.82 (0.68-0.98)	0.88 (0.67-1.15)
		Low PM _{2.5} ^c	High PM _{2.5} ^c	
Non-active commuting		1	1	
≤ two season of four		1.18 (0.94-1.49)	0.87 (0.69-1.10)	0.73 (0.53-1.01)
> two seasons of four		0.97 (0.80-1.19)	0.79 (0.65-0.95)	0.81 (0.62-1.06)

353 ^aAdjusted for sex, exposure year, education, smoking, alcohol intake, occupation, mean income, leisure time physical activity, and active commuting

354 ^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

355 ^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

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358 Individuals exposed to high concentrations of PM₁₀ and PM_{2.5} at their home address had a 14% and 1%
359 increased risk of incident IHD respectively, compared to individuals with low concentrations (Table 3).
360 These increased risks were, however, not statistically significant.

When including an interaction between particle concentrations and exercise, risk estimates showed a positive association between air pollution and IHD among individuals performing no exercise and those exercising no more than once a week, whereas a negative association was found among those exercising more than twice a week (Table 3). For PM₁₀ concentrations, an increased risk of 21% and 25% was observed among those who did not exercise or exercised at most once a week, respectively, whereas a decreased risk of 32% was estimated among those that exercised at least twice a week. Similarly, for PM_{2.5}, the risk of IHD increased by 16% among both those who did not exercise and those who exercised at most once a week, and decreased by 26% among those who exercised at least twice a week. The air pollution-associated risk was lower among those who exercised at least twice a week.

For active commuting, the highest air pollution-associated risk was found among those who did not perform any such activity, among whom the risks increased by a statistically significantly 26% and 24%, respectively (table 3). The risks were, however, not statistically significantly different from air pollution-associated risks among the active commuters (as presented in table 2).

Compared with individuals with low residential particle concentration, a high concentration of PM₁₀ was associated with 21% and 25% increased risk for IHD for those who never exercised in training clothes and those who exercised at most once a week, respectively, and showed a 32% decreased risk for those exercising at least twice a week; only the association for those exercising at most once a week was statistically significant. The corresponding estimates associated with PM_{2.5} are increased risk of IHD of 16% for those never exercising and those who exercised at most once a week, and a decreased risk of 26% among those exercising at least twice a week (Table 3); none of these associations was statistically significant.

IHD risk associated with high residential PM₁₀ and PM_{2.5} compared with low residential particle concentration was found to be 26% and 24% higher, respectively, among those never actively commuting; both these results were statistically significant. Among those actively commuting one or two seasons per year, IHD risk was 5% and 9% lower, respectively, while among those actively commuting more than two seasons out of four, the risk was 10% and 1% higher, respectively; none of these associations was significant. Overall, no statistically significant modifying effect of exercise and active commuting on the association between high particle concentration at home addresses and IHD was observed (Table3).

Table 3: Hazard ratios (95% CI) for IHD associated with high air pollution levels (vs low) at home address among persons with different exercise/commuting habits.

	Overall model with No interaction effects	Adjusted ^a HRs in different exercise categories		
		Exercise in training clothes		
		Never	≤ once/week	≥ twice/week
Low PM ₁₀ ^b	1	1	1	1
High PM ₁₀ ^b	1.14 (0.9-1.45)	1.21 (0.97-1.49)	1.25 (1.01-1.54)	0.68 (0.46-0.998)
Low PM _{2.5} ^c	1	1	1	1
High PM _{2.5} ^c	1.01 (0.8-1.28)	1.16 (0.94-1.44)	1.16 (0.95-1.43)	0.74 (0.51-1.09)
		Active commuting		
		Non-active commuting	≤ two season of four	> two seasons of four
Low PM ₁₀ ^c		1	1	1
High PM ₁₀ ^c		1.26 (1.03-1.54)	0.95 (0.7-1.29)	1.10 (0.86-1.41)
Low PM _{2.5} ^d		1	1	1
High PM _{2.5} ^d		1.24 (1.02-1.51)	0.91 (0.67-1.24)	1.01 (0.79-1.29)

^aAdjusted for sex, exposure year, education, smoking, alcohol intake, occupation, mean income, leisure time physical activity, active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

394 †Low PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

4 Discussion

Overall, we found increased risk of first incident IHD associated with air pollution at the home address but a protective effect of physical activity. A statistically significant beneficial effect of exercise was found among individuals with both high PM₁₀ and PM_{2.5}, but not among individuals with low levels. Also, for active commuting the benefits were greater among individuals with high residential particle concentrations, but these differences were not statistically significant. Air pollution concentration-associated risks were found among individuals who exercise at most once a week but not among individuals exercising at least twice a week. Statistically significantly increased risks were also found among non-active commuters. These risks were, however, not statistically significantly different from air pollution-associated risks among the active commuters.

Our findings are in accordance with a longitudinal cohort study on MI within the Danish Diet, Cancer, and Health cohort which found an increased benefit of participation in sports among individuals with high NO₂ concentration at the home addresses [16]. The reported risk reduction was 9, 15, and 24% respectively among individuals with low (<14.3 µg/m³), medium (14.3-21 µg/ m³) and high (>21 µg/ m³) residential NO₂ concentration. For walking and cycling they also estimated greater risk reductions for first incident MI among individuals with higher air pollution concentrations. In the same Danish cohort, the long term benefits of physical activity on CVD mortality were also found to be greater among individuals with high residential NO₂ [23]. The risk reduction associated with participation in cycling and gardening among individuals exposed to high residential NO₂ (≥ 19 µg/m³) was greater than those exposed to moderate/low NO₂ concentration (<19 µg/m³). Among participants exposed to high NO₂, the risk reduction for cycling and gardening was 30% and 23%, respectively, whereas among participants exposed to low NO₂, risk reduction was 17% and 15%, respectively. However, the interaction effects in these two studies were not statistically significant.

Opposite findings were observed for the modifying effect of physical activity on the association between air pollution and the incidence of diabetes [15]. Among the participants in the Danish cohort, the risk of developing diabetes increased by 10% per interquartile range of 4.9 mg/m³ residential NO₂ among physically active individuals, but there was no difference among less physically active individuals. The authors considered that this may be due to an additive rather multiplicative interaction, thus resulting in an increased risk estimate only among physical active individuals with a low risk of developing diabetes.

As inflammation is a causative mechanism for cardiovascular disease, we hypothesized that the anti-inflammatory effects of physical activity may reduce air pollution-associated risks since inflammation is one among several different pathways for the harmful health effects of air pollution. The findings of

greater benefits of physical activity among individuals with higher air pollution exposure for incident IHD risk in our study and incident MI and CVD mortality in the Danish cohort, support such a hypothesis. However, a study on physical activity and white blood cell counts conducted in a large cohort of Taiwanese adults suggested no effect modification by residential air pollution measured as PM_{2.5} [17]. Both physical activity and residential air pollution were, however, found to be associated with an inflammatory response assessed by white blood cell counts. However, the association between physical activity and white blood cell count is variable because exercise also causes a transient increase in white blood cell count which usually normalises within 24 hours [24]. The results of our study cannot be directly compared with the above mentioned studies due to the difference in pollutants [15,16,23] and health outcomes [15,16,23]. This study contributes with air pollution effect estimates on IHD incidence in a population with a relatively low level of air pollution concentrations. Compared with the previous cohort studies on interaction effects between air pollution and physical activity, the annual mean PM_{2.5} concentration was 3-4 times lower. The annual mean in the Taiwanese cohort was 27 µg/m³ and a recent study within the same population as the DHC-cohort studies reported 18 µg/m³. Even at these lower levels of air pollution an increased risk associated with air pollution exposure was found, however not among those who exercised at least twice a week. A major strength of our study is the air pollution particle concentration exposure data since particles are considered to be the causal component of air pollution [25]. The study used individual time varying exposures of annual mean concentrations during follow-up based on population address registries. The dispersion model used for modelling of particle concentrations has previously been validated [19]. Within the DHC studies NO₂ was used as a proxy for traffic generated air pollution and was assessed only at residential addresses at the year of recruitment or as an annual mean during follow-up. A limitation of our exposure data is that the statistical power only allowed for two exposure categories and therefore no exposure-response assessment was performed.

Another strength of our study is the prospective design, the long follow-up period, the large cohort size and the availability of baseline data on several important confounders. A limitation is the lack of information on the intensity and duration of physical activity and therefore only frequency of exercise could be considered. The study also lacked information on changes in physical activity and other life-style factors during follow-up.

There is a risk of reverse causation if individuals at their baseline examination had a low physical activity level due to poorer health. Furthermore, we lacked information on whether exercise is taking place outdoors or indoors. For active commuters we also lack air pollution exposure calculations during the commute. This would cause exposure misclassification among active commuters with a higher in-traffic air pollution exposure dose compared with non-active commuters, causing a possible bias to the null. This would also occur if individuals chose not to exercise outside during times with high air pollution exposure.

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5 Conclusion

The study estimated that exercise reduced the risk of first incident IHD, but only among individuals with higher residential particle concentrations (above median). Similarly, the harmful air pollution effect on IHD was only found among those who exercised less. Our results reinforce the public health message that physical activity is beneficial for cardiovascular health and thus support the adoption of strategies to improve health through promotion of physical activity and mitigation of air pollution. Further studies

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3 484 are needed to build on the evidence of physical activity and air pollution interactions on the incidence
4 485 cardiovascular disease. Air pollution exposures during commuting should also be considered in these
5 486 studies.
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13 490 **Author's contributions:** All the authors contributed to the study conception and design. W.R. and J.N.S.
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24

25 499 **Participants consent:** Obtained.
26

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	5
		(d) If applicable, explain how loss to follow-up was addressed	7
		(e) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-11
		(b) Report category boundaries when continuous variables were categorized	9, 11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Air pollution, physical activity and ischemic heart disease - A prospective cohort study of interaction effects

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30

31 Abstract

32 **Objective:** To assess a possible interaction effect between physical activity and air pollution on first
33 incidence of ischemic heart disease (IHD).

34 **Design:** Prospective cohort study

35 **Setting:** Umeå, Northern Sweden

36 **Participants:** We studied 34,748 adult participants of Västerbotten Intervention Programme cohort
37 from 1990 to January 2014. Annual particulate matter concentrations (PM_{2.5} and PM₁₀) at the
38 participants' residential addresses were modelled and a questionnaire on frequency of exercise and
39 active commuting was completed at baseline. Cox proportional hazards modelling was used to estimate
40 1) association with physical activity at different levels of air pollution, and 2) the association with
41 particulate matter at different levels of physical activity.

42 **Outcome:** First incidence of IHD.

43 **Results:** Over a mean follow-up of 12.4 years, there were 1,148 IHD cases. Overall, we observed an
44 increased risk of IHD among individuals with higher concentrations of particles at their home address.
45 Exercise at least twice a week was associated with a lower risk of IHD among participants with high
46 residential PM_{2.5} (0.60; 95% CI: 0.44-0.82) and PM₁₀ (0.55; 95% CI: 0.4-0.76). The same beneficial effect
47 was not observed with low residential PM_{2.5} (0.94; 95% CI: 0.72-1.22) and PM₁₀ (0.99; 95% CI: 0.76-1.29).
48 An increased risk associated with higher long-term exposure to particles was only observed among
49 participants never exercising in training clothes and among those not performing any active commuting.
50 However, only the interaction effect on hazard ratios for exercise was statistically significant.

51 **Conclusion:** Exercise was associated with a lower risk of first incidence of IHD among individuals with
52 higher residential particle concentrations. An air pollution-associated risk was only observed among
53 those who exercised less. The findings support the promotion of physical activity and a mitigation of air
54 pollution.

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56 **Key Words:** Air pollution, PM_{2.5}, PM₁₀, exercise, interaction, ischemic heart disease

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Strengths and limitations of this study

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- 66 • This study simultaneously evaluated the impact of physical activity and air pollution and their
67 interaction on first incident IHD cases in a population with relatively low level of air pollution
68 concentrations.
- 69 • For air pollution exposure, this study used individual time varying exposures of annual mean
70 concentrations during follow-up based on population address registries.
- 71 • Another strength is the prospective design and the availability of baseline data on several
72 important confounders.
- 73 • No exposure-response assessment could be performed since the statistical power only allowed
74 for the formation of two exposure categories.
- 75 • Differences in air pollution exposure during active commuting might cause biased estimates
76 due to exposure misclassification.

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1 Introduction

Cardiovascular disease (CVD) is the most important cause of morbidity and premature mortality worldwide, accounting for 422.3 million cases and 17.92 million deaths in 2015 [1]. There is solid evidence that inflammation is a key upstream pathogenic mechanism [2]. Ambient air pollution, generally comprising ozone, sulphur dioxide, nitrogen dioxide and particulate matter (PM), is a leading contributor to the global burden of disease and an important risk factor for morbidity and mortality. Particulate matter is often measured as $PM_{2.5}$, to represent particles with a diameter of 2.5 micrometres or less, and PM_{10} , to represent particles with a diameter of 10 micrometres or less. Ambient $PM_{2.5}$ exposure alone has been estimated to account for 4.2 million deaths in 2015, of which 1.5 million deaths were caused by ischemic heart diseases (IHD) [3]. The underlying mechanisms mediating the pathogenic impact of air pollution involve systemic oxidative stress and inflammation [4,5]. Physical activity is a salutogenic factor in numerous non-communicable chronic diseases (NCDs), with physical inactivity being responsible for 6% of the burden of disease from coronary heart disease [6,7]. The beneficial effects of physical activity include protection against low-grade inflammation by releasing anti-inflammatory substances, such as interleukin 6, from contracting muscles [8,9].

Rapid urbanization and increased use of motorized transport contribute to modern day problems such as traffic congestion, traffic related air pollution and lack of physical activity. Promotion of active transportation by changing mode of transport from car to cycling and walking are among the different strategies used to tackle these challenges [10–12]. As inflammation is a causative mechanism for cardiovascular disease, it is conceivable that the anti-inflammatory effects of physical activity may mitigate the harmful effects associated with exposure to air pollution. However, one major concern with physical activity in a polluted environment is the increased inhalation of particles due to an increase in respiratory volume that may counteract the beneficial effects of physical activity [13,14].

The long-term effects of air pollution among individuals with different levels of leisure time physical activity have been estimated within the Danish Diet, Cancer, and Health cohort. The incidence of diabetes was assessed in relation to leisure time physical activity and nitrogen dioxide (NO_2) concentration at the home address. Residential NO_2 was found to be associated with increased incidence of diabetes, but only among physically active individuals [15]. As far as we know, only one study has examined the modifying effect of air pollution on the association between physical activity and cardiovascular disease. In their recent study, Kubesch and colleagues conclude that physical activity reduced the risk of first incidence of myocardial infarction (MI) and recurrent MI among individuals with high NO_2 concentration at the residential addresses [16]. As only one pollutant (NO_2) and only one cardiovascular outcome (MI) have been studied, the knowledge of a possible interaction between air pollution and physical activity on CVD is inconclusive.

A Taiwanese study found an independent inverse association of habitual physical activity with inflammation across different levels of $PM_{2.5}$ exposure, although long term exposure was associated with increased inflammation at all levels of physical activity [17].

We therefore aimed to examine interaction effects between physical activity and long-term exposure to $PM_{2.5}$ and PM_{10} at residential addresses on the incidence of ischemic heart disease (IHD). We wanted to assess: 1) whether air pollution modifies the beneficial effects of physical activity on IHD, and 2) whether physical activity modifies the harmful effects of air pollution on IHD.

2 Methods

To determine the interaction effect between air pollution and physical activity on IHD incidence, we combined cohort data which comprised risk factors for IHD, national registry data on IHD incidence from the Swedish National Board of Health and Welfare, and yearly annual mean air pollution particle concentrations at the individuals' residential addresses using dispersion models from the Swedish Clean Air and Climate Research Program (SCAC).

VIP (Västerbotten Intervention Programme) is a population based screening and prospective cohort study, developed to reduce the risk of future CVD and diabetes by promoting a healthy lifestyle among individuals living in the Västerbotten region. The SCAC developed methods to estimate exposure to source-specific particulate matter such as PM_{2.5} and PM₁₀ and at residential addresses in Gothenborg, Stockholm and Umeå.

2.1 Study population

VIP is an ongoing population-based health investigation survey of all individuals at ages 40, 50 or 60 years, depending upon risk factors, living in the Västerbotten region, who are invited to participate in systematic risk factor screening and individual counselling about healthy lifestyle habits. A detailed description of VIP has been presented elsewhere [18]. Between 1990 and 2014, a total of 42,488 of the VIP participants that lived in Umeå Municipality during the study period were included in the analysis. After exclusion of 7,740 participants with missing information on exercise, the study sample thus consisted of 34,748 individuals, 53% men and 47% women, 40-60 years of age at baseline examination, with no previous history of IHD at time of enrolment. After exclusion of individuals with missing information on included confounders the final number of included individuals were 31424 and 29218 for the analyses of exercise in training clothes and active commuting, respectively. All participants in the VIP gave their informed written consent, and the study was approved by the Regional Ethics Review Board at Umea University (DNR: 2014-136-32M and 2015/16-31Ö).

2.2 Leisure time exercise and active commuting

The VIP questionnaire includes various self-reported information on physical activity including frequency of leisure time physical activity and active commuting (cycling or walking to and from work). The association with IHD was assessed in relation to frequency of exercise in training clothes and amounts of active commuting. Exercise during the previous three months was categorized as never, rarely, once per week, 2-3 times per week or more than 3 times per week. Based on this information, participants were categorized as "Twice per week or more" if they exercised with a frequency of 2-3 times per week and more, "At most once a week" if they exercised rarely or once per week, and "Never" if no activity was performed. For active commuting, participants were asked about their mode of transport to work each season. Participants were classified in three categories: "Non- active commuting" if commuting every season by car or bus, "At most two seasons out of four" if cycling or walking at most half a year and "More than two seasons out of four", if cycling and walking more than half a year.

193 2.3 Covariates

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195 The VIP questionnaire also gathered information on participants' educational status, occupation,
196 smoking, alcohol intake and economic status. Education was defined according to the International
197 Standard Classification of Education (ISCED), United Nations Educational, Scientific and Cultural
198 Organization (UNESCO) 1997. Participants were asked about the highest level education they had
199 achieved with eight predefined categories ranging from "pre-school" to "university education." Alcohol
200 intake was assessed by the reported frequency of consumption with answering options that ranged
201 from "Never" to "2-4 times/week." Information on smoking was gathered by using the question, "How
202 often do you smoke?" Information on occupational status was obtained with a question, "What kind of
203 job do you have nowadays?" with the answering options of eight predefined categories. Finally,
204 information on occupation status was asked with the question, "What is your current occupation?" with
205 8 categories ranging from permanently employed to retired.

207 2.4 Air pollution concentrations

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209 Annual mean total concentrations of PM_{2.5} and PM₁₀ for the years 1990-2011 (and thereafter linearly
210 extrapolated up until year 2014) were obtained from the SCAC research program, described in detail
211 elsewhere [19]. Briefly, concentrations of PM_{2.5} and PM₁₀ were estimated within SCAC by applying
212 dispersion models on local or regional emission inventories. These emission inventories contain detailed
213 information on emissions from different source categories, such as road traffic exhaust, road traffic non-
214 exhaust, domestic heating, shipping and industrial activities. For Umeå, inventories were validated
215 through monitoring for consistency. Emissions from small-scale residential heating were assessed using
216 registry data from chimney sweepers that included the type of wood stove or boiler. The addresses of
217 these residences were geocoded using the geographical centre coordinate of the estate. Road traffic
218 emission factors for PM exhaust for different vehicle types, speeds and driving conditions were
219 calculated based on the Handbook Emission Factors for Road Transport (HBEFA) version 3.1 [20].
220 Estimates for non-exhaust contribution from brake and tire wear were based on Omstedt et al. [21]. The
221 annual average emission from shipping was used in the modelling on a 1x1 km² grid resolution. The
222 emissions from other sources such as industrial processes, off-road machinery and agriculture was
223 collected from Swedish Meteorological and Hydrological Institute (SMHI). To obtain annual average
224 emissions of PM_{2.5} and PM₁₀, Gaussian models included in the Airviro air quality management system
225 (SMHI, 2010) were used for simulation based on hourly meteorological data for 1990, 2000 and 2011
226 [22]. The comparison between measured and modelled PM_{2.5} and PM₁₀ agreed well at most monitoring
227 stations ($r^2=0.87$ and $r^2=0.65$, respectively).

229 2.5 Outcome

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231 We linked the records in VIP and through the unique Swedish personal identification number with data
232 on first IHD event cases from the National Patient Register and the Cause of Death Register, both at the
233 National Board of Health and Welfare, using primary discharge diagnoses for IHD according to
234 International Classification of Diseases, 10th revision (ICD-10): code I20-125.

2.6 Patient and public involvement

No patients were involved in this study.

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2.7 Statistical Analysis

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We performed survival analyses using Cox regression proportion hazard model to estimate hazard ratios (HRs), and 95% confidence intervals (CIs), to estimate 1) the association between first incident IHD and air pollution exposure at different levels of physical activity and 2) the association between first incident IHD and physical activity at different levels of air pollution exposure. Age was used as the underlying timescale since it is a stronger confounder than calendar time. Follow-up started at date of recruitment to the cohort and ended with the earliest of the date of first IHD case, emigration, death, or 31 December 2013. Interaction between physical activity and air pollution and their impact on IHD was studied by introducing an interaction term into the model. Residential annual mean particle concentrations were used to calculate moving averages over the recent five years which were thereafter categorized as below or above the median concentration for PM_{2.5} and PM₁₀, respectively. Interaction with physical activity was assessed based on 1) the frequency of exercise in training clothes and 2) the number of seasons the individual walked or cycled to work. Active commuting by walking or cycling was categorized into three groups: non-active commuters, active commuters at most half of the year (up to two out of four seasons), active commuters more than half a year (more than two out of four seasons). Estimates were adjusted for: calendar year as a penalized cubic spline with 3 degrees of freedom, gender (male vs female), highest education level (compulsory, high school, university), alcohol intake (never, once/month or sometimes, 2-4 times/month, 2-3 times/week, ≥4 times/week), smoking (previous non-regular smoker, non-regular smoker, cigarette smoker, cigar or pipe smoker), occupation (gainfully employed, unemployed, not gainfully employed, retired), and registry data on area level mean income. In the basic model we adjusted only for gender and exposure year. All analyses were performed using R version 3.4.2, and the statistical inference was conducted with a 5% significance level. T-tests, global analysis of variance tests (ANOVA) and chi-square tests were used to test for differences in means and proportions of covariates between categories of exercise in training clothes (Table 1). The Schoenfeld residuals test was used to assess the assumption of proportional hazards. A sensitivity analysis was conducted by excluding participants with short follow-up time.

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3 Results

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The mean age at recruitment to this cohort was 45.8 years. Among the 34,748 participants 1,148 cases of IHD were identified during a mean follow-up time of 12.4 years. Of those cases, 500 never exercised, 529 exercised at most once a week and 119 exercised at least twice a week. Table 1 summarizes characteristics of participants according to different levels of leisure time physical activity. Participants not reporting any leisure time exercise were older and more likely to be male, non-commuters and to belong to a lower socioeconomic group. Subjects performing moderate to high-level physical activity, were more likely to be women, non-smokers, and active commuters. The 5-year mean of PM₁₀ and PM_{2.5} concentration were different between leisure time physical activity categories, with at most 7 and 6% difference respectively for PM₁₀ and PM_{2.5}.

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Table 1: Characteristics of participants at different levels of exercise in training clothes at baseline

Characteristics	Never	At most once a week	Twice per week or more	p
Exercise in training clothes n (%)	13043 (37.5)	14994 (43.2)	6711 (19.3)	
PM ₁₀ , µg/m ³ (mean (SD))	10.93 (2.00)	11.06 (1.96)	10.39 (1.94)	<0.001
PM _{2.5} , µg/m ³ (mean (SD))	6.41 (1.12)	6.49 (1.12)	6.11 (1.11)	<0.001
Frequency of active commuting (%)				<0.001
Non-active commuting	6369 (48.8)	6409 (42.7)	2666 (39.7)	
At most two seasons of four	1806 (13.8)	2547 (17.0)	1037 (15.5)	
More than two seasons of four	3506 (26.9)	4976 (33.2)	2555 (38.1)	
Missing	1362 (10.4)	1062 (7.1)	453 (6.8)	
Alcohol intake (%)				<0.001
Never	135 (1.0)	120 (0.8)	79 (1.2)	
Once/month or sometimes	5337 (40.9)	5950 (39.7)	2790 (41.6)	
2-4 times/month	2000 (15.3)	2436 (16.2)	1061 (15.8)	
2-3 times/week	97 (0.7)	93 (0.6)	54 (0.8)	
≥ 4 times/week	5068 (38.9)	5861 (39.1)	2265 (33.8)	
Missing	406 (3.1)	534 (3.6)	462 (6.9)	
Smoking (%)				<0.001
Never smoker	5139 (39.4)	7240 (48.3)	3467 (51.7)	
Previous non-regular smoker	1072 (8.2)	1458 (9.7)	711 (10.6)	
Non-regular smoker	581 (4.5)	807 (5.4)	348 (5.2)	
Previous regular smoker	2729 (20.9)	2865 (19.1)	1201 (17.9)	
Cigarette smoker	2789 (21.4)	1805 (12.0)	426 (6.3)	
Cigar or pipe smoker	186 (1.4)	130 (0.9)	45 (0.7)	
Missing	547 (4.2)	689 (4.6)	513 (7.6)	
Highest education level (%)				<0.001
Compulsory	5534 (42.4)	4319 (28.8)	1369 (20.4)	
High	3573 (27.4)	4116 (27.5)	1951 (29.1)	
University	3449 (26.4)	5933 (39.6)	2911 (43.4)	
Missing	487 (3.7)	626 (4.2)	480 (7.2)	
Gender %, (men)	7072 (54.2)	8036 (53.6)	3274 (48.8)	<0.001
Age, y (mean (SD))	47.28 (9.09)	45.27 (9.02)	44.32 (8.61)	<0.001
Occupation (%)	<0.001			
Gainfully employed	10536 (80.8)	12690 (84.6)	5452 (81.2)	
Unemployed	478 (3.7)	382 (2.5)	174 (2.6)	
Not gainfully employed	318 (2.4)	352 (2.3)	160 (2.4)	
Retired	673 (5.2)	449 (3.0)	194 (2.9)	
Missing	1038 (8.0)	1121 (7.5)	731 (10.9)	

Characteristics	Never	At most once a week	Twice per week or more	p
Mean income for the neighbourhood (SEK)	128285.70 (23017.70)	130332.22 (23875.04)	130221.55 (24605.92)	<0.001

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Compared with individuals who reported no exercise, those participants that exercised at least twice per week had a 24% lower risk of IHD (Table 2). The corresponding overall estimate associated with active commuting was a 13% reduced risk of IHD among individuals commuting more than two seasons per year.

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Allowing for an interaction between the frequency of exercise in training clothes and particle concentrations (PM₁₀ and PM_{2.5}) at the home address, the average 24% risk reduction from exercising at least twice per week was found to be driven by statistically significant interaction between exercise and particle exposure with 45% and 40% risk reduction among individuals with high PM₁₀ and PM_{2.5} concentrations, respectively (table 2). The interaction coefficients estimating the additional benefit of exercise among individuals with a high PM₁₀ concentration at their home addresses were a 3% increased risk among those who exercised at most once a week whereas a decreased risk of 44% was estimated among those who exercised at least twice a week. The corresponding estimates among those with high PM_{2.5} concentrations were a risk reduction of 0% and 36% respectively.

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For active commuters with low particle exposure at their home address, the risk of incident IHD was 17% and 18% higher among those commuting one or two seasons per year and 7% and 3% lower among those commuting at least two seasons per year, for PM₁₀ and PM_{2.5} respectively. The benefit of active commuting was larger among individuals with a high particle concentration at their home address: risk reductions for active commuting during one or two seasons were 12% and 13% and for more than two seasons 18% and 21% respectively, compared with non-active commuters. No statistically significant interaction was found between active commuting and particle concentrations at the home address.

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Table 2: Hazard ratios (95% CI) for IHD associated with different exercise and commuting habits among persons with different air pollution exposure at home addresses.

Exercise in training clothes	Overall model with no interaction effects	Proportional hazard p-value*	Adjusted ^a HRs in categories of high and low particle exposure				Adjusted ^a interaction hazard ratio	Proportional hazard p-value ^d
			Low PM ₁₀ ^b		High PM ₁₀ ^b			
Never	1		1		1		1.03 (0.81-1.32)	0.75
≤ once/week	1.03 (0.90-1.16)	0.35	1.01 (0.84-1.21)	0.67	1.04 (0.88-1.23)	0.35	0.56 (0.37-0.84)	0.65

≥ twice/week	0.76 (0.62-0.93)	0.08	0.99 (0.76-1.29)	0.47	0.55 (0.40-0.76)	0.24		
			Low PM _{2.5} ^c		High PM _{2.5} ^c			
Never			1		1		1.00 (0.78-1.28)	0.61
≤ once/week			1.03 (0.86-1.23)	0.78	1.03 (0.87-1.22)	0.30	0.64 (0.43-0.96)	0.30
≥ twice/week			0.94 (0.72-1.22)	0.69	0.60 (0.44-0.82)	0.09		
Active commuting per season			Low PM ₁₀ ^b		High PM ₁₀ ^b			
Non-active commuting	1		1		1			
≤ two seasons of four	1.01 (0.86-1.19)	0.50	1.17 (0.93-1.47)	0.35	0.88 (0.70-1.11)	0.70	0.76 (0.55-1.04)	0.34
> two seasons of four	0.87 (0.76-0.998)	0.85	0.93 (0.76-1.14)	0.48	0.82 (0.68-0.98)	0.89	0.88 (0.67-1.15)	0.53
			Low PM _{2.5} ^c		High PM _{2.5} ^c			
Non-active commuting			1		1			
≤ two seasons of four			1.18 (0.94-1.49)	0.43	0.87 (0.69-1.10)	0.76	0.73 (0.53-1.01)	0.43
> two seasons of four			0.97 (0.80-1.19)	0.37	0.79 (0.65-0.95)	0.89	0.81 (0.62-1.06)	0.44

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^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity, and active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

^d p-value of the Schoenfeld residual test of proportional hazards

335 Individuals exposed to high concentrations of PM₁₀ and PM_{2.5} at their home address had a 14% and 1%
336 increased risk of incident IHD respectively, compared to individuals with low concentrations (Table 3).
337 These increased risks were, however, not statistically significant.

338 When including an interaction between particle concentrations and exercise, risk estimates showed a
339 positive association between air pollution and IHD among individuals performing no exercise and those
340 exercising no more than once a week, whereas a negative association was found among those exercising
341 more than twice a week (Table 3).

342 Compared with individuals with low residential particle concentration, a high concentration of PM₁₀ was
343 associated with 21% and 25% increased risk for IHD for those who never exercised in training clothes
344 and those who exercised at most once a week, respectively, and showed a 32% decreased risk for those
345 exercising at least twice a week; only the association for those exercising at most once a week was
346 statistically significant. The corresponding estimates associated with PM_{2.5} are increased risk of IHD of
347 16% for those never exercising and those who exercised at most once a week, and a decreased risk of
348 26% among those exercising at least twice a week (Table 3); none of these associations was statistically
349 significant.

IHD risk associated with high residential PM₁₀ and PM_{2.5} compared with low residential particle concentration was found to be 26% and 24% higher, respectively, among those never actively commuting; both these results were statistically significant. Among those actively commuting one or two seasons per year, IHD risk was 5% and 9% lower, respectively, while among those actively commuting more than two seasons out of four, the risk was 10% and 1% higher, respectively; none of these risks were, however, statistically significantly different from the air pollution-associated risks among the active commuters (Table 2). Overall, no statistically significant modifying effect of exercise and active commuting on the association between high particle concentration at home addresses and IHD was observed (Table 3).

Excluding participants with short follow-up time did not affect the main conclusions of our study, however estimates tended to be lower for overall effect of air pollution on IHD (Supplementary file A: Table 2).

Table 3: Hazard ratios (95% CI) for IHD associated with high air pollution levels (vs low) at home address among persons with different exercise/commuting habits.

	Overall model with no interaction effects	Proportional hazard p-value ^d	Adjusted ^a HRs in categories of high and low particle exposure					
			Exercise in training clothes		Active commuting		P-value	
			Never	Proportional hazard p-value ^d	≤ once/week	Proportional hazard p-value ^d	≥ twice/week	Proportional hazard p-value ^d
Low PM ₁₀ ^b	1		1		1		1	
High PM ₁₀ ^b	1.14 (0.9-1.45)	0.55	1.21 (0.97-1.49)	0.71	1.25 (1.01-1.54)	0.45	0.68 (0.46-0.998)	0.50
Low PM _{2.5} ^c	1		1		1		1	
High PM _{2.5} ^c	1.01 (0.8-1.28)	1.10	1.16 (0.94-1.44)	0.38	1.16 (0.95-1.43)	0.13	0.74 (0.51-1.09)	0.11
			Non-active commuting		≤ two seasons of four		> two seasons of four	
Low PM ₁₀ ^b			1		1		1	
High PM ₁₀ ^b			1.26 (1.03-1.54)	0.39	0.95 (0.7-1.29)	0.66	1.10 (0.86-1.41)	0.17
Low PM _{2.5} ^c			1		1		1	
High PM _{2.5} ^c			1.24 (1.02-1.51)	0.11	0.91 (0.67-1.24)	0.84	1.01 (0.79-1.29)	0.04

^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity, active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

^d p-value of the Schoenfeld residual test of proportional hazards

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4 Discussion

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386 Overall, we found increased risk of first incident IHD associated with air pollution at the home address
387 but a protective effect of physical activity. A statistically significant beneficial effect of exercise was
388 found among individuals with high PM10/PM2.5, but not among individuals with low levels. Also, for
389 active commuting the benefits were greater among individuals with high residential particle
390 concentrations, but these differences were not statistically significant. Air pollution concentration-
391 associated risks were found among individuals who exercise at most once a week but not among
392 individuals exercising at least twice a week. Statistically significantly increased risks were also found
393 among non-active commuters. These risks were, however, not statistically significantly different from air
394 pollution-associated risks among the active commuters.

395 Our findings are in accordance with a longitudinal cohort study on MI within the Danish Diet, Cancer,
396 and Health cohort which found an increased benefit of participation in sports among individuals with
397 high NO₂ concentration at the home addresses [16]. The reported risk reduction was 9, 15, and 24%
398 respectively among individuals with low (<14.3 µg/m³), medium (14.3-21 µg/ m³) and high (>21 µg/ m³)
399 residential NO₂ concentration. For walking and cycling they also estimated greater risk reductions for
400 first incident MI among individuals with higher air pollution concentrations. In the same Danish cohort,
401 the long term benefits of physical activity on CVD mortality were also found to be greater among
402 individuals with high residential NO₂ [23]. The risk reduction associated with participation in cycling and
403 gardening among individuals exposed to high residential NO₂ (≥ 19 µg/m³) was greater than those
404 exposed to moderate/low NO₂ concentration (<19 µg/m³). Among participants exposed to high NO₂, the
405 risk reduction for cycling and gardening was 30% and 23%, respectively, whereas among participants
406 exposed to low NO₂, risk reduction was 17% and 15%, respectively. However, the interaction effects in
407 these two studies were not statistically significant.

408 Opposite findings were observed for the modifying effect of physical activity on the association between
409 air pollution and the incidence of diabetes [15]. Among the participants in the Danish cohort, the risk of
410 developing diabetes increased by 10% per interquartile range of 4.9 mg/m³ residential NO₂ among
411 physically active individuals, but there was no difference among less physically active individuals. The
412 authors considered that this may be due to an additive rather multiplicative interaction, thus resulting in
413 an increased risk estimate only among physical active individuals with a low risk of developing diabetes.

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416 As inflammation is a causative mechanism for cardiovascular disease, we hypothesized that the anti-
417 inflammatory effects of physical activity may reduce air pollution-associated risks since inflammation is
418 one among several different pathways for the harmful health effects of air pollution. The findings of
419 greater benefits of physical activity among individuals with higher air pollution exposure for incident IHD

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3 420 risk in our study and incident MI and CVD mortality in the Danish cohort, support such a hypothesis.
4 421 However, a study on physical activity and white blood cell counts conducted in a large cohort of
5 422 Taiwanese adults suggested no effect modification by residential air pollution measured as PM_{2.5} [17].
6 423 Both physical activity and residential air pollution were, however, found to be associated with an
7 424 inflammatory response assessed by white blood cell counts. However, the association between physical
8 425 activity and white blood cell count is variable because exercise also causes a transient increase in white
9 426 blood cell count which usually normalises within 24 hours [24]. The results of our study cannot be
10 427 directly compared with the above mentioned studies due to the difference in pollutants [15,16,23] and
11 428 health outcomes [15,16,23]. This study contributes with air pollution effect estimates on IHD incidence
12 429 in a population with a relatively low level of air pollution concentrations. Compared with the previous
13 430 cohort studies on interaction effects between air pollution and physical activity, the annual mean PM_{2.5}
14 431 concentration was 3-4 times lower. The annual mean in the Taiwanese cohort was 27 µg/m³ and a
15 432 recent study within the same population as the DHC-cohort studies reported 18 µg/m³. Even at these
16 433 lower levels of air pollution an increased risk associated with air pollution exposure was found, however
17 434 not among those who exercised at least twice a week. Even though active commuting may result in
18 435 higher air pollution exposure compared with for instance driving a car to work, the risk of an IHD event
19 436 was still reduced since the benefit of the physical activity was greater than the IHD risk imposed by the
20 437 air pollution exposure.
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25 439 A major strength of our study is the air pollution particle concentration exposure data since particles are
26 440 considered to be the causal component of air pollution [25]. The study used individual time varying
27 441 exposures of annual mean concentrations during follow-up based on population address registries. The
28 442 dispersion model used for modelling of particle concentrations has previously been validated [19].
29 443 Within the DHC studies NO₂ was used as a proxy for traffic generated air pollution and was assessed only
30 444 at residential addresses at the year of recruitment or as an annual mean during follow-up. A limitation
31 445 of our exposure data is that the statistical power only allowed for two exposure categories and
32 446 therefore no exposure-response assessment was performed.
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35 447 Another strength of our study is the prospective design, the long follow-up period, the large cohort size
36 448 and the availability of baseline data on several important confounders. A limitation is the lack of
37 449 information on the intensity and duration of physical activity and therefore only frequency of exercise
38 450 could be considered. The study also lacked information on changes in physical activity and other life-
39 451 style factors during follow-up as the information was only retrieved at baseline.
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41 452 There is a risk of reverse causation if individuals at their baseline examination had a low physical activity
42 453 level due to poorer health. Individuals could for instance have diseases that affect their risk to later in
43 454 life have an IHD event (such as diabetes) prior to baseline examination. If this prior disease also affected
44 455 the frequency the individual exercised in training clothes, or mode of commuting, then a reverse
45 456 causation between physical activity and IHD risk may occur. Individuals with a prior IHD event at
46 457 baseline were however excluded. Furthermore, we lacked information on whether exercise is taking
47 458 place outdoors or indoors. For active commuters we also lack air pollution exposure calculations during
48 459 the commute. This would cause exposure misclassification among active commuters with a higher in-
49 460 traffic air pollution exposure dose compared with non-active commuters, causing a possible bias to the
50 461 null. This would also occur if individuals chose not to exercise outside during times with high air
51 462 pollution exposure.
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5 Conclusion

The study estimated that exercise reduced the risk of first incident IHD, but only among individuals with higher residential particle concentrations (above median). Similarly, the harmful air pollution effect on IHD was only found among those who exercised less. Our results reinforce the public health message that physical activity is beneficial for cardiovascular health and thus support the adoption of strategies to improve health through promotion of physical activity and mitigation of air pollution. Further studies are needed to build on the evidence of physical activity and air pollution interactions on the incidence cardiovascular disease. Air pollution exposures during commuting should also be considered in these studies.

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Author's contributions: All the authors contributed to the study conception and design. W.R. and J.N.S. analysed the data. W.R wrote the first draft of the manuscript. B.F., B.K. and J.N.S. critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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Competing interests: None.

Participants consent: Obtained.

Ethics approval: The study was approved by the Regional Ethics Review Board at Umea University (DNR: 2014-136-32M and 2015/16-31Ö).

Data availability: No additional data is available

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A: Sensitivity analysis by excluding the individuals with follow-up time below the 25th percentile

Table 1. Hazard ratios (95% CI) for IHD associated with different exercise and commuting habits among persons with different air pollution exposure at home addresses.

Exercise in training clothes	Overall model with no interaction effects	Adjusted ^a HRs in categories of high and low particle exposure		Adjusted ^a interaction hazard ratio
		Low PM ₁₀ ^b	High PM ₁₀ ^b	
		Low PM ₁₀ ^b	High PM ₁₀ ^b	Benefits of exercise/commuting comparing high and low particle exposure
Never	1	1	1	
≤ once/week	1.00 (0.84-1.19)	1.01 (0.84-1.21)	1.02 (0.85-1.23)	1.02 (0.79-1.31)
≥ twice/week	0.88 (0.76-1.02)	1.0 (0.77-1.31)	0.48 (0.34-0.7)	0.48 (0.31-0.76)
		Low PM _{2.5} ^c	High PM _{2.5} ^c	
Never	1	1	1	
≤ once/week		1.01 (0.84-1.21)	1.02 (0.85-1.23)	1.01 (0.78-1.31)
≥ twice/week		0.95 (0.72-1.24)	0.53 (0.37-0.75)	0.56 (0.36-0.87)
Active commuting per season		Low PM ₁₀ ^b	High PM ₁₀ ^b	
Non-active commuting	1	1	1	
≤ two seasons of four	1.02 (0.89-1.16)	1.16 (0.92-1.46)	0.85 (0.66-1.09)	0.73 (0.52-1.03)
> two seasons of four	0.74 (0.6-0.92)	0.91 (0.74-1.12)	0.83 (0.68-1.02)	0.91 (0.69-1.2)
		Low PM _{2.5} ^c	High PM _{2.5} ^c	
Non-active commuting		1	1	
≤ two seasons of four		1.18 (0.93-1.48)	0.84 (0.65-1.08)	0.70 (0.50-0.98)
> two seasons of four		0.98 (0.80-1.2)	0.79 (0.64-0.96)	0.82 (0.62-1.09)

^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity, active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

Table 2. Hazard ratios (95% CI) for IHD associated with high air pollution levels (vs low) at home address among persons with different exercise/commuting habits.

	Overall model with No interaction effects	Adjusted ^a HRs in different exercise categories		
		Exercise in training clothes		
		Never	≤ once/week	≥ twice/week
Low PM ₁₀ ^b	1	1	1	1
High PM ₁₀ ^b	1.22 (0.96-1.56)	1.25 (1.0-1.56)	1.27 (1.03-1.58)	0.61 (0.40-0.93)
Low PM _{2.5} ^c	1	1	1	1
High PM _{2.5} ^c	0.95 (0.74-1.21)	1.15 (0.92-1.43)	1.16 (0.94-1.44)	0.64 (0.42-0.97)
		Active commuting		
		Non-active commuting	≤ two seasons of four	> two seasons of four
Low PM ₁₀ ^b		1	1	1
High PM ₁₀ ^b		1.28 (1.04-1.57)	0.94 (0.68-1.29)	1.16 (0.9-1.5)
Low PM _{2.5} ^c		1	1	1
High PM _{2.5} ^c		1.23 (1.0-1.51)	0.88 (0.64-1.21)	0.99 (0.76-1.27)

^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity, active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

B1: Distributions of PM10 and PM2.5 moving averages (lag 1-5) for the person-years included in the study

Figure 1: PM10 distribution

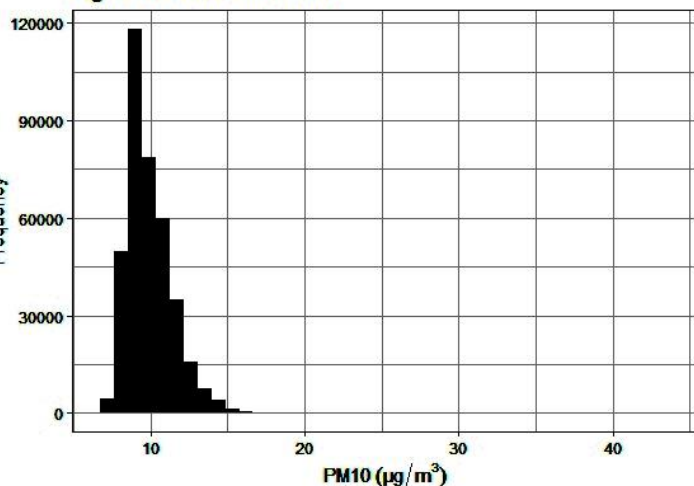
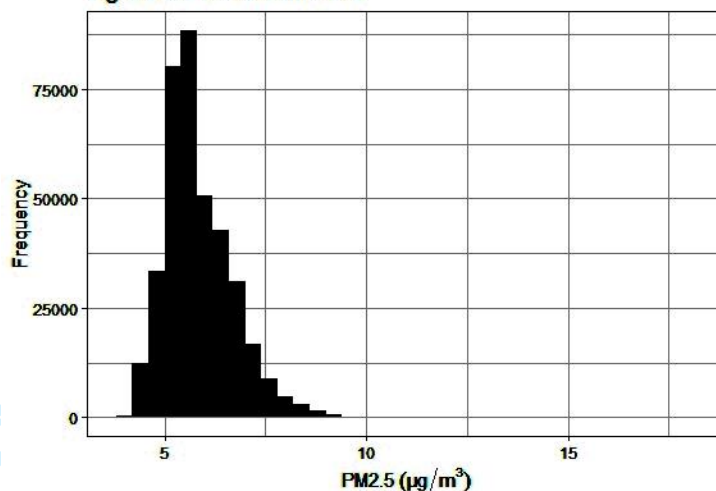


Figure 2: PM2.5 distribution



B2: Distributions of PM10 and PM2.5 moving averages (lag 1-5) for the person-years included in the study at different levels of physical activity (exercise in training clothes).

Figure 3: PM10 at different levels of exercise

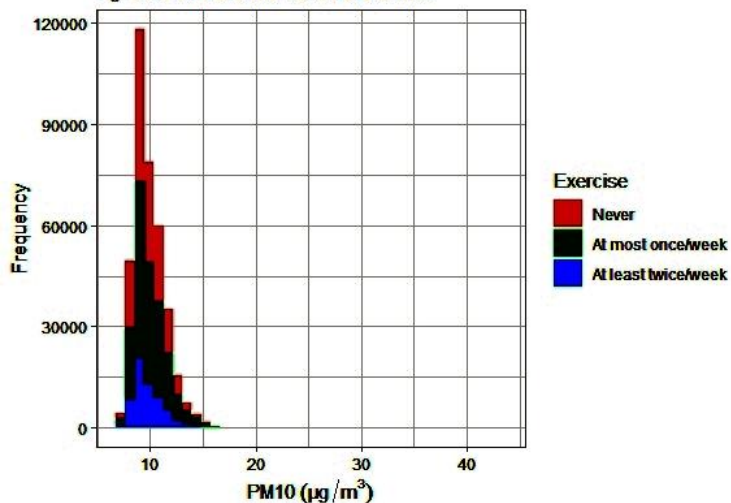
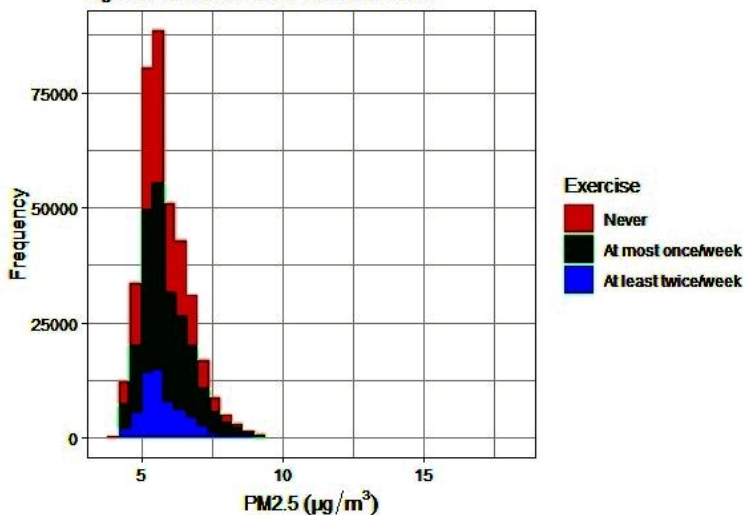


Figure 4: PM2.5 at different levels of exercise



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	5
		(d) If applicable, explain how loss to follow-up was addressed	7
		(e) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-11
		(b) Report category boundaries when continuous variables were categorized	9, 11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Air pollution, physical activity and ischemic heart disease - A prospective cohort study of interaction effects

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30

31 Abstract

32 **Objective:** To assess a possible interaction effect between physical activity and air pollution on first
33 incidence of ischemic heart disease (IHD).

34 **Design:** Prospective cohort study

35 **Setting:** Umeå, Northern Sweden

36 **Participants:** We studied 34,748 adult participants of Västerbotten Intervention Programme cohort
37 from 1990 to January 2014. Annual particulate matter concentrations (PM_{2.5} and PM₁₀) at the
38 participants' residential addresses were modelled and a questionnaire on frequency of exercise and
39 active commuting was completed at baseline. Cox proportional hazards modelling was used to estimate
40 1) association with physical activity at different levels of air pollution, and 2) the association with
41 particulate matter at different levels of physical activity.

42 **Outcome:** First incidence of IHD.

43 **Results:** Over a mean follow-up of 12.4 years, there were 1,148 IHD cases. Overall, we observed an
44 increased risk of IHD among individuals with higher concentrations of particles at their home address.
45 Exercise at least twice a week was associated with a lower risk of IHD among participants with high
46 residential PM_{2.5} (0.60; 95% CI: 0.44-0.82) and PM₁₀ (0.55; 95% CI: 0.4-0.76). The same beneficial effect
47 was not observed with low residential PM_{2.5} (0.94; 95% CI: 0.72-1.22) and PM₁₀ (0.99; 95% CI: 0.76-1.29).
48 An increased risk associated with higher long-term exposure to particles was only observed among
49 participants never exercising in training clothes and among those not performing any active commuting.
50 However, only the interaction effect on hazard ratios for exercise was statistically significant.

51 **Conclusion:** Exercise was associated with a lower risk of first incidence of IHD among individuals with
52 higher residential particle concentrations. An air pollution-associated risk was only observed among
53 those who exercised less. The findings support the promotion of physical activity and a mitigation of air
54 pollution.

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56 **Key Words:** Air pollution, PM_{2.5}, PM₁₀, exercise, interaction, ischemic heart disease

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Strengths and limitations of this study

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- 66 • This study simultaneously evaluated the impact of physical activity and air pollution and their
67 interaction on first incident IHD cases in a population with relatively low level of air pollution
68 concentrations.
- 69 • For air pollution exposure, this study used individual time varying exposures of annual mean
70 concentrations during follow-up based on population address registries.
- 71 • Another strength is the prospective design and the availability of baseline data on several
72 important confounders.
- 73 • No exposure-response assessment could be performed since the statistical power only allowed
74 for the formation of two exposure categories.
- 75 • Differences in air pollution exposure during active commuting might cause biased estimates due
76 to exposure misclassification.

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1 Introduction

Cardiovascular disease (CVD) is the most important cause of morbidity and premature mortality worldwide, accounting for 422.3 million cases and 17.92 million deaths in 2015 [1]. There is solid evidence that inflammation is a key upstream pathogenic mechanism [2]. Ambient air pollution, generally comprising ozone, sulphur dioxide, nitrogen dioxide and particulate matter (PM), is a leading contributor to the global burden of disease and an important risk factor for morbidity and mortality. Particulate matter is often measured as PM_{2.5}, to represent particles with a diameter of 2.5 micrometres or less, and PM₁₀, to represent particles with a diameter of 10 micrometres or less. Ambient PM_{2.5} exposure alone has been estimated to account for 4.2 million deaths in 2015, of which 1.5 million deaths were caused by ischemic heart diseases (IHD) [3]. The underlying mechanisms mediating the pathogenic impact of air pollution involve systemic oxidative stress and inflammation [4,5]. Physical activity is a salutogenic factor in numerous non-communicable chronic diseases (NCDs), with physical inactivity being responsible for 6% of the burden of disease from coronary heart disease [6,7]. The beneficial effects of physical activity include protection against low-grade inflammation by releasing anti-inflammatory substances, such as interleukin 6, from contracting muscles [8,9].

Rapid urbanization and increased use of motorized transport contribute to modern day problems such as traffic congestion, traffic related air pollution and lack of physical activity. Promotion of active transportation by changing mode of transport from car to cycling and walking are among the different strategies used to tackle these challenges [10–12]. As inflammation is a causative mechanism for cardiovascular disease, it is conceivable that the anti-inflammatory effects of physical activity may mitigate the harmful effects associated with exposure to air pollution. However, one major concern with physical activity in a polluted environment is the increased inhalation of particles due to an increase in respiratory volume that may counteract the beneficial effects of physical activity [13,14].

The long-term effects of air pollution among individuals with different levels of leisure time physical activity have been estimated within the Danish Diet, Cancer, and Health cohort. The incidence of diabetes was assessed in relation to leisure time physical activity and nitrogen dioxide (NO₂) concentration at the home address. Residential NO₂ was found to be associated with increased incidence of diabetes, but only among physically active individuals [15]. As far as we know, only one study has examined the modifying effect of air pollution on the association between physical activity and cardiovascular disease. In their recent study, Kubesch and colleagues conclude that physical activity reduced the risk of first incidence of myocardial infarction (MI) and recurrent MI among individuals with high NO₂ concentration at the residential addresses [16]. As only one pollutant (NO₂) and only one cardiovascular outcome (MI) have been studied, the knowledge of a possible interaction between air pollution and physical activity on CVD is inconclusive.

A Taiwanese study found an independent inverse association of habitual physical activity with inflammation across different levels of PM_{2.5} exposure, although long term exposure was associated with increased inflammation at all levels of physical activity [17].

We therefore aimed to examine interaction effects between physical activity and long-term exposure to PM_{2.5} and PM₁₀ at residential addresses on the incidence of ischemic heart disease (IHD). We wanted to assess: 1) whether air pollution modifies the beneficial effects of physical activity on IHD, and 2) whether physical activity modifies the harmful effects of air pollution on IHD.

2 Methods

To determine the interaction effect between air pollution and physical activity on IHD incidence, we combined cohort data which comprised risk factors for IHD, national registry data on IHD incidence from the Swedish National Board of Health and Welfare, and yearly annual mean air pollution particle concentrations at the individuals' residential addresses using dispersion models from the Swedish Clean Air and Climate Research Program (SCAC).

VIP (Västerbotten Intervention Programme) is a population based screening and prospective cohort study, developed to reduce the risk of future CVD and diabetes by promoting a healthy lifestyle among individuals living in the Västerbotten region. The SCAC developed methods to estimate exposure to source-specific particulate matter such as PM_{2.5} and PM₁₀ and at residential addresses in Gothenburg, Stockholm and Umeå.

2.1 Study population

VIP is an ongoing population-based health investigation survey of all individuals at ages 40, 50 or 60 years, depending upon risk factors, living in the Västerbotten region, who are invited to participate in systematic risk factor screening and individual counselling about healthy lifestyle habits. A detailed description of VIP has been presented elsewhere [18]. Between 1990 and 2014, a total of 42,488 of the VIP participants that lived in Umeå Municipality during the study period were included in the analysis. After exclusion of 7,740 participants with missing information on exercise, the study sample thus consisted of 34,748 individuals, 53% men and 47% women, 40-60 years of age at baseline examination, with no previous history of IHD at time of enrolment. After exclusion of individuals with missing information on included confounders the final number of included individuals were 31424 and 29218 for the analyses of exercise in training clothes and active commuting, respectively. All participants in the VIP gave their informed written consent, and the study was approved by the Regional Ethics Review Board at Umea University (DNR: 2014-136-32M and 2015/16-31Ö).

2.2 Leisure time exercise and active commuting

The VIP questionnaire includes various self-reported information on physical activity including frequency of leisure time physical activity and active commuting (cycling or walking to and from work). The association with IHD was assessed in relation to frequency of exercise in training clothes and amounts of active commuting. Exercise during the previous three months was categorized as never, rarely, once per week, 2-3 times per week or more than 3 times per week. Based on this information, participants were categorized as "Twice per week or more" if they exercised with a frequency of 2-3 times per week and more, "At most once a week" if they exercised rarely or once per week, and "Never" if no activity was performed. For active commuting, participants were asked about their mode of transport to work each season. Participants were classified in three categories: "Non- active commuting" if commuting every season by car or bus, "At most two seasons out of four" if cycling or walking at most half a year and "More than two seasons out of four", if cycling and walking more than half a year.

193 2.3 Covariates

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195 The VIP questionnaire also gathered information on participants' educational status, occupation,
196 smoking, alcohol intake and economic status. Education was defined according to the International
197 Standard Classification of Education (ISCED), United Nations Educational, Scientific and Cultural
198 Organization (UNESCO) 1997. Participants were asked about the highest level education they had
199 achieved with eight predefined categories ranging from "pre-school" to "university education." Alcohol
200 intake was assessed by the reported frequency of consumption with answering options that ranged
201 from "Never" to "2-4 times/week." Information on smoking was gathered by using the question, "How
202 often do you smoke?" Information on occupational status was obtained with a question, "What kind of
203 job do you have nowadays?" with the answering options of eight predefined categories. Finally,
204 information on occupation status was asked with the question, "What is your current occupation?" with
205 8 categories ranging from permanently employed to retired.

207 2.4 Air pollution concentrations

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209 Annual mean total concentrations of PM_{2.5} and PM₁₀ for the years 1990-2011 (and thereafter linearly
210 extrapolated up until year 2014) were obtained from the SCAC research program, described in detail
211 elsewhere [19]. Briefly, concentrations of PM_{2.5} and PM₁₀ were estimated within SCAC by applying
212 dispersion models on local or regional emission inventories. These emission inventories contain detailed
213 information on emissions from different source categories, such as road traffic exhaust, road traffic non-
214 exhaust, domestic heating, shipping and industrial activities. For Umeå, inventories were validated
215 through monitoring for consistency. Emissions from small-scale residential heating were assessed using
216 registry data from chimney sweepers that included the type of wood stove or boiler. The addresses of
217 these residences were geocoded using the geographical centre coordinate of the estate. Road traffic
218 emission factors for PM exhaust for different vehicle types, speeds and driving conditions were
219 calculated based on the Handbook Emission Factors for Road Transport (HBEFA) version 3.1 [20].
220 Estimates for non-exhaust contribution from brake and tire wear were based on Omstedt et al. [21]. The
221 annual average emission from shipping was used in the modelling on a 1x1 km² grid resolution. The
222 emissions from other sources such as industrial processes, off-road machinery and agriculture was
223 collected from Swedish Meteorological and Hydrological Institute (SMHI). To obtain annual average
224 emissions of PM_{2.5} and PM₁₀, Gaussian models included in the Airviro air quality management system
225 (SMHI, 2010) were used for simulation based on hourly meteorological data for 1990, 2000 and 2011
226 [22]. The comparison between measured and modelled PM_{2.5} and PM₁₀ agreed well at most monitoring
227 stations ($r^2=0.87$ and $r^2=0.65$, respectively).

229 2.5 Outcome

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231 We linked the records in VIP and through the unique Swedish personal identification number with data
232 on first IHD event cases from the National Patient Register and the Cause of Death Register, both at the
233 National Board of Health and Welfare, using primary discharge diagnoses for IHD according to
234 International Classification of Diseases, 10th revision (ICD-10): code I20-125.

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2.6 Patient and public involvement

No patients were involved in this study.

2.7 Statistical Analysis

We performed survival analyses using Cox regression proportion hazard model to estimate hazard ratios (HRs), and 95% confidence intervals (CIs), to estimate 1) the association between first incident IHD and air pollution exposure at different levels of physical activity and 2) the association between first incident IHD and physical activity at different levels of air pollution exposure. Age was used as the underlying timescale since it is a stronger confounder than calendar time. Follow-up started at date of recruitment to the cohort and ended with the earliest of the date of first IHD case, emigration, death, or 31 December 2013. Interaction between physical activity and air pollution and their impact on IHD was studied by introducing an interaction term into the model. Residential annual mean particle concentrations were used to calculate moving averages over the recent five years which were thereafter categorized as below or above the median concentration for PM_{2.5} and PM₁₀, respectively. Sensitivity analyses were also performed with PM concentrations categorized by tertiles. Interaction with physical activity was assessed based on 1) the frequency of exercise in training clothes and 2) the number of seasons the individual walked or cycled to work. Active commuting by walking or cycling was categorized into three groups: non-active commuters, active commuters at most half of the year (up to two out of four seasons), active commuters more than half a year (more than two out of four seasons). Estimates were adjusted for a pre-specified set of covariates: calendar year as a penalized cubic spline with 3 degrees of freedom, gender (male vs female), highest education level (compulsory, high school, university), alcohol intake (never, once/month or sometimes, 2-4 times/month, 2-3 times/week, ≥ 4 times/week), smoking (previous non-regular smoker, non-regular smoker, cigarette smoker, cigar or pipe smoker), occupation (gainfully employed, unemployed, not gainfully employed, retired), and registry data on area level mean income year 1994. In the basic model we adjusted only for gender and exposure year. All analyses were performed using R version 3.4.2, and the statistical inference was conducted with a 5% significance level. T-tests, global analysis of variance tests (ANOVA) and chi-square tests were used to test for differences in means and proportions of covariates between categories of exercise in training clothes (Table 1). The Schoenfeld residuals test was used to assess the assumption of proportional hazards. A sensitivity analysis was conducted by excluding participants with follow-up time below the 25th percentile.

3 Results

The mean age at recruitment to this cohort was 45.8 years. Among the 34,748 participants 1,148 cases of IHD were identified during a mean follow-up time of 12.4 years. Of those cases, 500 never exercised, 529 exercised at most once a week and 119 exercised at least twice a week. Table 1 summarizes characteristics of participants according to different levels of leisure time physical activity. Participants not reporting any leisure time exercise were older and more likely to be male, non-commuters and to belong to a lower socioeconomic group. Subjects performing moderate to high-level physical activity,

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279 were more likely to be women, non-smokers, and active commuters. The 5-year means of PM₁₀ and
280 PM_{2.5} concentrations were different between leisure time physical activity categories, with at most 7
281 and 6% difference respectively for PM₁₀ and PM_{2.5} (with distributions presented in Supplemental
282 material A: Figures 1-4).

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Table 1: Characteristics of participants at different levels of exercise in training clothes at baseline

Characteristics	Never	At most once a week	Twice per week or more	p
Exercise in training clothes n (%)	13043 (37.5)	14994 (43.2)	6711 (19.3)	
PM ₁₀ , µg/m ³ (mean (SD))	10.93 (2.00)	11.06 (1.96)	10.39 (1.94)	<0.001
PM _{2.5} , µg/m ³ (mean (SD))	6.41 (1.12)	6.49 (1.12)	6.11 (1.11)	<0.001
Frequency of active commuting (%)				<0.001
Non-active commuting	6369 (48.8)	6409 (42.7)	2666 (39.7)	
At most two seasons of four	1806 (13.8)	2547 (17.0)	1037 (15.5)	
More than two seasons of four	3506 (26.9)	4976 (33.2)	2555 (38.1)	
Missing	1362 (10.4)	1062 (7.1)	453 (6.8)	
Alcohol intake (%)				<0.001
Never	135 (1.0)	120 (0.8)	79 (1.2)	
Once/month or sometimes	5337 (40.9)	5950 (39.7)	2790 (41.6)	
2-4 times/month	2000 (15.3)	2436 (16.2)	1061 (15.8)	
2-3 times/week	97 (0.7)	93 (0.6)	54 (0.8)	
≥ 4 times/week	5068 (38.9)	5861 (39.1)	2265 (33.8)	
Missing	406 (3.1)	534 (3.6)	462 (6.9)	
Smoking (%)				<0.001
Never smoker	5139 (39.4)	7240 (48.3)	3467 (51.7)	
Previous non-regular smoker	1072 (8.2)	1458 (9.7)	711 (10.6)	
Non-regular smoker	581 (4.5)	807 (5.4)	348 (5.2)	
Previous regular smoker	2729 (20.9)	2865 (19.1)	1201 (17.9)	
Cigarette smoker	2789 (21.4)	1805 (12.0)	426 (6.3)	
Cigar or pipe smoker	186 (1.4)	130 (0.9)	45 (0.7)	
Missing	547 (4.2)	689 (4.6)	513 (7.6)	
Highest education level (%)				<0.001
Compulsory	5534 (42.4)	4319 (28.8)	1369 (20.4)	
High	3573 (27.4)	4116 (27.5)	1951 (29.1)	
University	3449 (26.4)	5933 (39.6)	2911 (43.4)	
Missing	487 (3.7)	626 (4.2)	480 (7.2)	
Gender %, (men)	7072 (54.2)	8036 (53.6)	3274 (48.8)	<0.001
Age, y (mean (SD))	47.3 (9.1)	45.3 (9.0)	44.3 (8.6)	<0.001
Occupation (%)	<0.001			
Gainfully employed	10536 (80.8)	12690 (84.6)	5452 (81.2)	
Unemployed	478 (3.7)	382 (2.5)	174 (2.6)	
Not gainfully employed	318 (2.4)	352 (2.3)	160 (2.4)	
Retired	673 (5.2)	449 (3.0)	194 (2.9)	
Missing	1038 (8.0)	1121 (7.5)	731 (10.9)	
Mean income for the neighbourhood (SEK*) (mean (SD))	128286 (23018)	130332 (23875)	130222 (24606)	<0.001

*SEK=Swedish krona

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3 298 Compared with individuals who reported no exercise, those participants that exercised at least twice per
4 299 week had a 24% lower risk of IHD (Table 2). The corresponding overall estimate associated with active
5 300 commuting was a 13% reduced risk of IHD among individuals commuting more than two seasons per
6 301 year.

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9 302 Allowing for an interaction between the frequency of exercise in training clothes and particle
10 303 concentrations (PM_{10} and $PM_{2.5}$) at the home address, the average 24% risk reduction from exercising at
11 304 least twice per week was found to be driven by statistically significant interaction between exercise and
12 305 particle exposure with 45% and 40% risk reduction among individuals with high PM_{10} and $PM_{2.5}$
13 306 concentrations, respectively (table 2). The interaction coefficients estimating the additional benefit of
14 307 exercise among individuals with a high PM_{10} concentration at their home addresses were a 3% increased
15 308 risk among those who exercised at most once a week whereas a decreased risk of 44% was estimated
16 309 among those who exercised at least twice a week. The corresponding estimates among those with high
17 310 $PM_{2.5}$ concentrations were a risk reduction of 0% and 36% respectively.

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20 311 For active commuters with low particle exposure at their home address, the risk of incident IHD was 17%
21 312 and 18% higher among those commuting one or two seasons per year and 7% and 3% lower among
22 313 those commuting at least two seasons per year, for PM_{10} and $PM_{2.5}$ respectively. The benefit of active
23 314 commuting was larger among individuals with a high particle concentration at their home address: risk
24 315 reductions for active commuting during one or two seasons were 12% and 13% and for more than two
25 316 seasons 18% and 21% respectively, compared with non-active commuters. No statistically significant
26 317 interaction was found between active commuting and particle concentrations at the home address.

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322 Table 2: Hazard ratios (95% CI) for IHD associated with different exercise and commuting habits among persons with
 323 different air pollution exposure at home addresses.
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Exercise in training clothes	Overall model with no interaction effects	Proportional hazard p-value*	Adjusted ^a HRs in categories of high and low particle exposure				Adjusted ^a interaction hazard ratio	
			Low PM ₁₀ ^b	Proportional hazard p-value ^d	High PM ₁₀ ^b	Proportional hazard p-value ^d	Benefits of exercise/commuting comparing high and low particle exposure	Proportional hazard p-value ^d
Never	1		1		1			
≤ once/week	1.03 (0.90-1.16)	0.35	1.01 (0.84-1.21)	0.67	1.04 (0.88-1.23)	0.35	1.03 (0.81-1.32)	0.75
≥ twice/week	0.76 (0.62-0.93)	0.08	0.99 (0.76-1.29)	0.47	0.55 (0.40-0.76)	0.24	0.56 (0.37-0.84)	0.65
			Low PM _{2.5} ^c		High PM _{2.5} ^c			
Never			1		1			
≤ once/week			1.03 (0.86-1.23)	0.78	1.03 (0.87-1.22)	0.30	1.00 (0.78-1.28)	0.61
≥ twice/week			0.94 (0.72-1.22)	0.69	0.60 (0.44-0.82)	0.09	0.64 (0.43-0.96)	0.30
Active commuting per season			Low PM ₁₀ ^b		High PM ₁₀ ^b			
Non-active commuting	1		1		1			
≤ two seasons of four	1.01 (0.86-1.19)	0.50	1.17 (0.93-1.47)	0.35	0.88 (0.70-1.11)	0.70	0.76 (0.55-1.04)	0.34
> two seasons of four	0.87 (0.76-0.998)	0.85	0.93 (0.76-1.14)	0.48	0.82 (0.68-0.98)	0.89	0.88 (0.67-1.15)	0.53
			Low PM _{2.5} ^c		High PM _{2.5} ^c			
Non-active commuting			1		1			
≤ two seasons of four			1.18 (0.94-1.49)	0.43	0.87 (0.69-1.10)	0.76	0.73 (0.53-1.01)	0.43
> two seasons of four			0.97 (0.80-1.19)	0.37	0.79 (0.65-0.95)	0.89	0.81 (0.62-1.06)	0.44

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 327 ^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity,
 328 and active
 329 commuting

330 ^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

331 ^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

332 ^d p-value of the Schoenfeld residual test of proportional hazards
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344 Individuals exposed to high concentrations of PM₁₀ and PM_{2.5} at their home address had a 14% and 1%
345 increased risk of incident IHD respectively, compared to individuals with low concentrations (Table 3).
346 These increased risks were, however, not statistically significant.

347 When including an interaction between particle concentrations and exercise, risk estimates showed a
348 positive association between air pollution and IHD among individuals performing no exercise and those
349 exercising no more than once a week, whereas a negative association was found among those exercising
350 more than twice a week (Table 3).

351 Compared with individuals with low residential particle concentration, a high concentration of PM₁₀ was
352 associated with 21% and 25% increased risk for IHD for those who never exercised in training clothes
353 and those who exercised at most once a week, respectively, and showed a 32% decreased risk for those
354 exercising at least twice a week; only the association for those exercising at most once a week was
355 statistically significant. The corresponding estimates associated with PM_{2.5} are increased risk of IHD of
356 16% for those never exercising and those who exercised at most once a week, and a decreased risk of
357 26% among those exercising at least twice a week (Table 3); none of these associations was statistically
358 significant.

359 IHD risk associated with high residential PM₁₀ and PM_{2.5} compared with low residential particle
360 concentration was found to be 26% and 24% higher, respectively, among those never actively
361 commuting; both these results were statistically significant. Among those actively commuting one or
362 two seasons per year, IHD risk was 5% and 9% lower, respectively, while among those actively
363 commuting more than two seasons out of four, the risk was 10% and 1% higher, respectively; none of
364 these risks were, however, statistically significantly different from the air pollution-associated risks
365 among the active commuters (Table 2). Overall, no statistically significant modifying effect of exercise
366 and active commuting on the association between high particle concentration at home addresses and
367 IHD was observed (Table 3).

368 Sensitivity analyses

369 Excluding participants with short follow-up time (below the 25th percentile of 3.4 years) did not affect
370 the main conclusions of our study, however estimates tended to be lower for overall effect of air
371 pollution on IHD (Supplementary material B: Tables 1 and 2).

372 Sensitivity analyses were also conducted with PM concentrations in tertiles. An indication of a dose-
373 response was found, with increasing benefits of exercise in training clothes with higher levels of PM
374 concentrations at the home address (Supplementary material C: Table 3). Exercising at least twice per
375 week (compared with never) reduced the risk of incident IHD by 5, 17, and 49% within the first, second
376 and third tertile of PM₁₀ exposure, respectively. Similar risk reductions were found in relation to tertiles
377 of PM_{2.5}.

378 No such interaction dose-response was however found for risks associated with PM exposure. Risk
379 estimates associated with PM were somewhat higher among individuals that exercised once a week
380 compared those who never exercised, whereas no increased risk associated with either PM₁₀ or PM_{2.5}
381 was found among individuals that exercised at least twice per week (Supplementary material C: Table 4).
382 A dose-response with increasing risks for IHD were found with both PM₁₀ and PM_{2.5} among those that
383 never exercised.

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3 384 These interactions between PM concentrations and exercise at least twice per week (compared with
4 385 never) were statistically significant for PM10 and borderline statistically significant for PM2.5
5 386 (Supplementary material C: Table 5).
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389 Table 3: Hazard ratios (95% CI) for IHD associated with high air pollution levels (vs low) at home address among persons with
 390 different exercise/commuting habits.
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	Overall model with no interaction effects	Proportional hazard p-value ^d	Adjusted ^a HRs in categories of high and low particle exposure					
			Exercise in training clothes					
			Never	Proportional hazard p-value ^d	≤ once/week	Proportional hazard p-value ^d	≥ twice/week	Proportional hazard p-value ^d
Low PM ₁₀ ^b	1		1		1		1	
High PM ₁₀ ^b	1.14 (0.9-1.45)	0.55	1.21 (0.97-1.49)	0.71	1.25 (1.01-1.54)	0.45	0.68 (0.46-0.998)	0.50
Low PM _{2.5} ^c	1		1		1		1	
High PM _{2.5} ^c	1.01 (0.8-1.28)	1.10	1.16 (0.94-1.44)	0.38	1.16 (0.95-1.43)	0.13	0.74 (0.51-1.09)	0.11
Active commuting								
			Non-active commuting		≤ two seasons of four	P-value	> two seasons of four	
Low PM ₁₀ ^b			1		1		1	
High PM ₁₀ ^b			1.26 (1.03-1.54)	0.39	0.95 (0.7-1.29)	0.66	1.10 (0.86-1.41)	0.17
Low PM _{2.5} ^c			1		1		1	
High PM _{2.5} ^c			1.24 (1.02-1.51)	0.11	0.91 (0.67-1.24)	0.84	1.01 (0.79-1.29)	0.04

^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity, active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

^d p-value of the Schoenfeld residual test of proportional hazards

4 Discussion

Overall, we found increased risk of first incident IHD associated with air pollution at the home address but a protective effect of physical activity. A statistically significant beneficial effect of exercise was found among individuals with high PM₁₀/PM_{2.5}, but not among individuals with low levels. Also, for active commuting the benefits were greater among individuals with high residential particle concentrations, but these differences were not statistically significant. Air pollution concentration-associated risks were found among individuals who exercise at most once a week but not among individuals exercising at least twice a week. Statistically significantly increased risks were also found among non-active commuters. These risks were, however, not statistically significantly different from air pollution-associated risks among the active commuters.

Our findings are in accordance with a longitudinal cohort study on MI within the Danish Diet, Cancer, and Health cohort which found an increased benefit of participation in sports among individuals with high NO₂ concentration at the home addresses [16]. The reported risk reduction was 9, 15, and 24% respectively among individuals with low (<14.3 µg/m³), medium (14.3-21 µg/m³) and high (>21 µg/m³) residential NO₂ concentration. For walking and cycling they also estimated greater risk reductions for first incident MI among individuals with higher air pollution concentrations. In the same Danish cohort, the long term benefits of physical activity on CVD mortality were also found to be greater among individuals with high residential NO₂ [23]. The risk reduction associated with participation in cycling and gardening among individuals exposed to high residential NO₂ (≥ 19 µg/m³) was greater than those exposed to moderate/low NO₂ concentration (<19 µg/m³). Among participants exposed to high NO₂, the risk reduction for cycling and gardening was 30% and 23%, respectively, whereas among participants exposed to low NO₂, risk reduction was 17% and 15%, respectively. However, the interaction effects in these two studies were not statistically significant.

Opposite findings were observed for the modifying effect of physical activity on the association between air pollution and the incidence of diabetes [15]. Among the participants in the Danish cohort, the risk of developing diabetes increased by 10% per interquartile range of 4.9 mg/m³ residential NO₂ among physically active individuals, but there was no difference among less physically active individuals. The authors considered that this may be due to an additive rather multiplicative interaction, thus resulting in an increased risk estimate only among physical active individuals with a low risk of developing diabetes.

As inflammation is a causative mechanism for cardiovascular disease, we hypothesized that the anti-inflammatory effects of physical activity may reduce air pollution-associated risks since inflammation is one among several different pathways for the harmful health effects of air pollution. The findings of greater benefits of physical activity among individuals with higher air pollution exposure for incident IHD risk in our study and incident MI and CVD mortality in the Danish cohort, support such a hypothesis. However, a study on physical activity and white blood cell counts conducted in a large cohort of Taiwanese adults suggested no effect modification by residential air pollution measured as PM_{2.5} [17]. Both physical activity and residential air pollution were, however, found to be associated with an inflammatory response assessed by white blood cell counts. However, the association between physical activity and white blood cell count is variable because exercise also causes a transient increase in white blood cell count which usually normalises within 24 hours [24]. The results of our study cannot be directly compared with the above mentioned studies due to the difference in pollutants [15,16,23] and health outcomes [15,16,23]. This study contributes with air pollution effect estimates on IHD incidence in a population with a relatively low level of air pollution concentrations. Compared with the previous

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3 455 cohort studies on interaction effects between air pollution and physical activity, the annual mean PM_{2.5}
4 456 concentration was 3-4 times lower. The annual mean in the Taiwanese cohort was 27 µg/m³ and a
5 457 recent study within the same population as the DHC-cohort studies reported 18 µg/m³. Even at these
6 458 lower levels of air pollution an increased risk associated with air pollution exposure was found, however
7 459 not among those who exercised at least twice a week. Even though active commuting may result in
8 460 higher air pollution exposure compared with for instance driving a car to work, the risk of an IHD event
9 461 was still reduced since the benefit of the physical activity was greater than the IHD risk imposed by the
10 462 air pollution exposure.
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12 464 A major strength of our study is the air pollution particle concentration exposure data since particles are
13 465 considered to be the causal component of air pollution [25]. The study used individual time varying
14 466 exposures of annual mean concentrations during follow-up based on population address registries. The
15 467 dispersion model used for modelling of particle concentrations has previously been validated [19].
16 468 Within the DHC studies NO₂ was used as a proxy for traffic generated air pollution and was assessed only
17 469 at residential addresses at the year of recruitment or as an annual mean during follow-up. A limitation
18 470 of our exposure data is that the statistical power only allowed for two exposure categories and
19 471 therefore no exposure-response assessment was performed.

20 472 Another strength of our study is the prospective design, the long follow-up period, the large cohort size
21 473 and the availability of baseline data on several important confounders. A limitation is the lack of
22 474 information on the intensity and duration of physical activity and therefore only frequency of exercise
23 475 could be considered. The study also lacked information on changes in physical activity and other life-
24 476 style factors during follow-up as the information was only retrieved at baseline.

25 477 There is a risk of reverse causation if individuals at their baseline examination had a low physical activity
26 478 level due to poorer health. Individuals could for instance have diseases that affect their risk to later in
27 479 life have an IHD event (such as diabetes) prior to baseline examination. If this prior disease also affected
28 480 the frequency the individual exercised in training clothes, or mode of commuting, then a reverse
29 481 causation between physical activity and IHD risk may occur. Individuals with a prior IHD event at
30 482 baseline were however excluded, and the sensitivity analyses that excluded individuals with follow-up
31 483 time below the 25th percentile showed that this did not change the results. Furthermore, we lacked
32 484 information on whether exercise is taking place outdoors or indoors. For active commuters we also lack
33 485 air pollution exposure calculations during the commute. This would cause exposure misclassification
34 486 among active commuters with a higher in-traffic air pollution exposure dose compared with non-active
35 487 commuters, causing a possible bias to the null. This would also occur if individuals chose not to exercise
36 488 outside during times with high air pollution exposure.

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5 Conclusion

The study estimated that exercise reduced the risk of first incident IHD, but only among individuals with higher residential particle concentrations (above median). Similarly, the harmful air pollution effect on IHD was only found among those who exercised less. Our results reinforce the public health message that physical activity is beneficial for cardiovascular health and thus support the adoption of strategies to improve health through promotion of physical activity and mitigation of air pollution. Further studies are needed to build on the evidence of physical activity and air pollution interactions on the incidence cardiovascular disease. Air pollution exposures during commuting should also be considered in these studies.

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Author's contributions: All the authors contributed to the study conception and design. W.R. and J.N.S. analysed the data. W.R wrote the first draft of the manuscript. B.F., B.K. and J.N.S. critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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Competing interests: None.

Participants consent: Obtained.

Ethics approval: The study was approved by the Regional Ethics Review Board at Umea University (DNR: 2014-136-32M and 2015/16-31Ö).

Data availability: No additional data is available

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A1: Distributions of PM10 and PM2.5 moving averages (lag 1-5) for the person-years included in the study

Figure 1: PM10 distribution

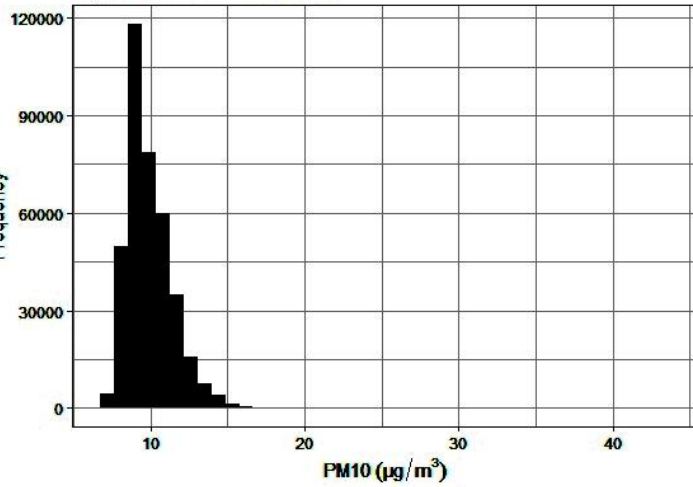
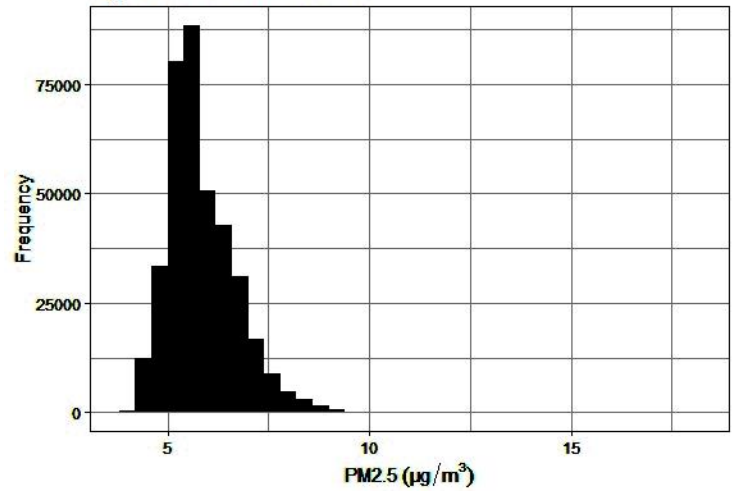


Figure 2: PM2.5 distribution



A2: Distributions of PM10 and PM2.5 moving averages (lag 1-5) for the person-years included in the study at different levels of physical activity (exercise in training clothes).

Figure 3: PM10 at different levels of exercise

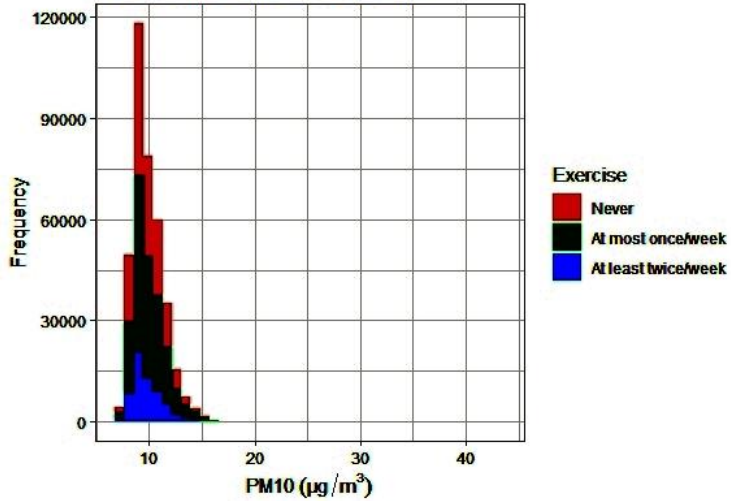
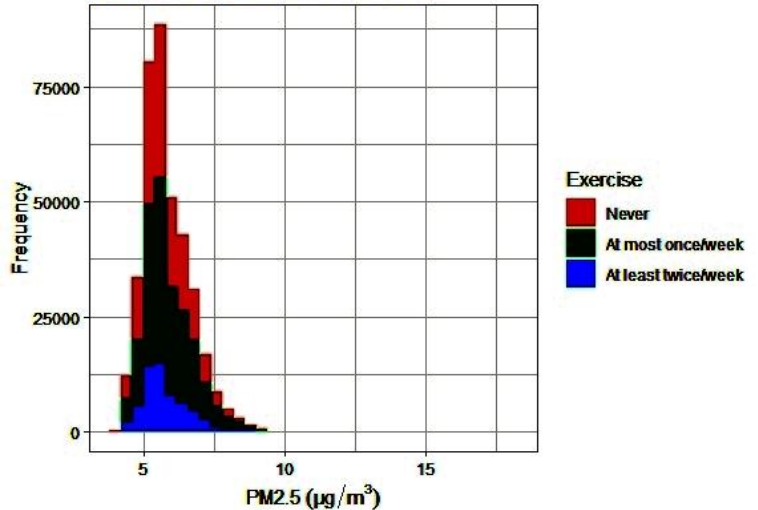


Figure 4: PM2.5 at different levels of exercise



B: Sensitivity analysis by excluding the individuals with follow-up time below the 25th percentile

Table 1. Hazard ratios (95% CI) for IHD associated with different exercise and commuting habits among persons with different air pollution exposure at home addresses.

Exercise in training clothes	Overall model with no interaction effects	Adjusted ^a HRs in categories of high and low particle exposure		Adjusted ^a interaction hazard ratio
		Low PM ₁₀ ^b	High PM ₁₀ ^b	
				Benefits of exercise/commuting comparing high and low particle exposure
Never	1	1	1	
≤ once/week	1.00 (0.84-1.19)	1.01 (0.84-1.21)	1.02 (0.85-1.23)	1.02 (0.79-1.31)
≥ twice/week	0.88 (0.76-1.02)	1.0 (0.77-1.31)	0.48 (0.34-0.7)	0.48 (0.31-0.76)
		Low PM _{2.5} ^c	High PM _{2.5} ^c	
Never		1	1	
≤ once/week		1.01 (0.84-1.21)	1.02 (0.85-1.23)	1.01 (0.78-1.31)
≥ twice/week		0.95 (0.72-1.24)	0.53 (0.37-0.75)	0.56 (0.36-0.87)
Active commuting per season		Low PM ₁₀ ^b	High PM ₁₀ ^b	
Non-active commuting	1	1	1	
≤ two seasons of four	1.02 (0.89-1.16)	1.16 (0.92-1.46)	0.85 (0.66-1.09)	0.73 (0.52-1.03)
> two seasons of four	0.74 (0.6-0.92)	0.91 (0.74-1.12)	0.83 (0.68-1.02)	0.91 (0.69-1.2)
		Low PM _{2.5} ^c	High PM _{2.5} ^c	
Non-active commuting		1	1	
≤ two seasons of four		1.18 (0.93-1.48)	0.84 (0.65-1.08)	0.70 (0.50-0.98)
> two seasons of four		0.98 (0.80-1.2)	0.79 (0.64-0.96)	0.82 (0.62-1.09)

^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity, active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

Table 2. Hazard ratios (95% CI) for IHD associated with high air pollution levels (vs low) at home address among persons with different exercise/commuting habits.

	Overall model with No interaction effects	Adjusted ^a HRs in different exercise categories		
		Exercise in training clothes		
		Never	≤ once/week	≥ twice/week
Low PM ₁₀ ^b	1	1	1	1
High PM ₁₀ ^b	1.22 (0.96-1.56)	1.25 (1.0-1.56)	1.27 (1.03-1.58)	0.61 (0.40-0.93)
Low PM _{2.5} ^c	1	1	1	1
High PM _{2.5} ^c	0.95 (0.74-1.21)	1.15 (0.92-1.43)	1.16 (0.94-1.44)	0.64 (0.42-0.97)
		Active commuting		
		Non-active commuting	≤ two seasons of four	> two seasons of four
Low PM ₁₀ ^b		1	1	1
High PM ₁₀ ^b		1.28 (1.04-1.57)	0.94 (0.68-1.29)	1.16 (0.9-1.5)
Low PM _{2.5} ^c		1	1	1
High PM _{2.5} ^c		1.23 (1.0-1.51)	0.88 (0.64-1.21)	0.99 (0.76-1.27)

^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity, active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

C: Sensitivity analyses with PM10 and PM2.5 concentrations categorized by tertile limits

Table 3. Hazard ratios (95% CI) for IHD associated with different exercise and commuting habits among persons with different air pollution exposure at home addresses.

Exercise in training clothes	Overall model with no interaction effects	Proportional hazard p ^d -value*	Adjusted ^a HRs in categories of high and low particle exposure					
			Low PM ₁₀ ^b	Proportional hazard p-value ^d	Moderate PM ₁₀ ^b	Proportional hazard p-value ^d	High PM ₁₀ ^b	Proportional hazard p-value ^d
Never	1		1		1			
≤ once/week	1.03 (0.90-1.16)	0.36	0.93 (0.74-1.16)	0.42	1.15 (0.94-1.41)	0.95	0.99 (0.80-1.23)	0.37
≥ twice/week	0.76 (0.62-0.93)	0.09	0.95 (0.68-1.32)	0.54	0.83 (0.60-1.15)	0.16	0.51 (0.34-0.77)	0.86
			Low PM _{2.5} ^c		Moderate PM _{2.5} ^c		High PM _{2.5} ^c	
Never			1		1			
≤ once/week			0.98 (0.78-1.22)	0.67	1.08 (0.88-1.32)	0.60	1.02 (0.82-1.26)	0.48
≥ twice/week			0.91 (0.65-1.27)	0.71	0.83 (0.60-1.14)	0.13	0.54 (0.36-0.82)	0.60

^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity, and active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

^dp-value of the Schoenfeld residual test of proportional hazards

Table 4. Hazard ratios (95% CI) for IHD associated with high and moderate air pollution levels (vs low) at home address among persons with different exercise/commuting habits.

	Overall model with no interaction effects	Proportional hazard p-value ^d	Adjusted ^a HRs in categories of high and low particle exposure					
			Exercise in training clothes					
			Never	Proportional hazard p-value ^d	≤ once/week	Proportional hazard p-value ^d	≥ twice/week	Proportional hazard p-value ^d
Low PM ₁₀ ^b	1		1		1		1	
Moderate PM ₁₀ ^b	1.04 (0.81-1.34)	0.55	1.05 (0.83 - 1.32)	0.35	1.30 (1.03 - 1.63)	0.95	0.92 (0.61-1.39)	0.26
High PM ₁₀ ^b	1.00 (0.69-1.45)	0.99	1.16 (0.87 - 1.53)	0.13	1.23 (0.93-1.64)	0.13	0.62 (0.37-1.04)	0.56
Low PM _{2.5} ^c	1		1		1		1	
Moderate PM ₁₀ ^b	1.12 (0.88-1.43)	0.94	1.11 (0.89 - 1.39)	0.73	1.23 (0.98-1.53)	0.73	1.02 (0.67-1.54)	0.30
High PM _{2.5} ^c	1.15 (0.79-1.68)	0.13	1.18 (0.89 - 1.57)	0.05	1.23 (0.92-1.64)	0.04	0.71 (0.42-1.18)	0.22

^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity, and active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

^dp-value of the Schoenfeld residual test of proportional hazards

Table 5. Interaction hazard ratios between exercise and air pollution for incident IHD

Exercise in training clothes	Adjusted ^a interaction hazard ratio			
	Benefits of exercise comparing moderate with low particle exposure		Benefits of exercise comparing high with low particle exposure	
	Moderate PM ₁₀ ^b	Proportional hazard p-value ^d	High PM ₁₀ ^b	Proportional hazard p-value ^d
Never	1		1	
≤ once/week	1.24 (0.91-1.68)	0.51	1.07 (0.78-1.45)	0.99
≥ twice/week	0.88 (0.55-1.39)	0.58	0.54 (0.32-0.92)	0.81
	Benefits of exercise comparing high with low PM _{2.5} ^b exposure		Benefits of exercise comparing moderate with low PM _{2.5} ^b exposure	
Never	1		1	
≤ once/week	1.11 (0.82-1.50)	0.97	1.04 (0.77-1.42)	0.87
≥ twice/week	0.92 (0.58-1.46)	0.45	0.60 (0.35-1.02)	0.87

^aAdjusted for sex, calendar year, education, smoking, alcohol intake, occupation, neighbourhood mean income, leisure time physical activity, and active commuting

^bLow PM₁₀: ≤9.6 µg/m³; High PM₁₀: >9.6 µg/m³

^cLow PM_{2.5} ≤5.7 µg/m³; High PM_{2.5}: >5.7 µg/m³

^dp-value of the Schoenfeld residual test of proportional hazards

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	5
		(d) If applicable, explain how loss to follow-up was addressed	7
		(e) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-11
		(b) Report category boundaries when continuous variables were categorized	9, 11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.