Glycocalyx, cardiometabolic disease and inflammation

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Publication date
2011

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Physical activity, Metabolic Syndrome and Coronary Risk: The EPIC-Norfolk Prospective Population Study

European Journal for Cardiovascular Prevention & Rehabilitation; 2011 Apr;18(2):209-17

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Abstract

Objective: We investigated the association between physical activity, the metabolic syndrome (MS), and the risk of future coronary heart disease (CHD) and mortality due to CHD in middle-aged men and women.

Design: Prospective cohort study.

Subjects: A total of 10134 men and women aged 45-79 years at baseline, were selected from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk cohort. Cardiovascular risk factors and physical activity levels were recorded at baseline. Rates of CHD and CHD mortality were recorded during a follow-up of 10.9 years.

Results: The prevalence of MS was 37.6% in men and 30.2% in women. Hazard ratios (HR) for future CHD were 1.95 (95%CI 1.65-2.31) for men with MS and 3.17 (95%CI 2.53-3, 97) for women with MS, compared to those without MS. HR adjusted for age and smoking were 1.52 (95%CI 1.29-1.81) for men and 1.76 (95%CI 1.39-2.23) for women. Additional adjustment for physical activity did not attenuate these risk estimates further (HR 1.51 (95%CI 1.27-1.79) and 1.74 (95%CI 1.38-2.21), respectively. CHD risk associated with MS was substantially lower among participants who were physically active. There was no longer a significant difference in CHD event rate between men with MS who were active and men without MS who were inactive (11.5% vs. 12.8%). For women, similar associations were observed (5.3% vs. 5.6%). We found evidence for significant effect modification (p for interaction = 0.006) such that physical activity affected the association between MS and CHD risk.

Conclusion: Middle-aged men and women with MS have an increased risk for future CHD. This CHD risk associated with MS is substantially lower among those who are physically active. Participants with MS who were physically active had a lower CHD risk than people without MS who were physically inactive.

Introduction

The global epidemic of obesity heralds an explosion of new-onset metabolic syndrome (MS) [1]. MS is defined as the combined presence of three or more of the following risk factors: glucose intolerance, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol (HDL-C), hypertension and abdominal obesity. Increased intra-abdominal and ectopic fat accumulation favours the development of this clustering of atherogenic risk factors, which is associated with a substantially increased risk of cardiovascular morbidity and mortality [2, 3]. There is an ongoing debate about the value of MS in predicting cardiovascular risk. Among the topics of this debate, the question arises whether the increased cardiovascular risk is similar for every person meeting the diagnostic criteria for MS [4-6]. Studies have reported that physical inactivity is associated with most if not all components of MS [7]. Consequently, physical inactivity is associated with a higher risk for coronary events which is in part due to a deterioration of established cardiovascular risk factors associated with MS. Even without weight loss, regular physical exercise has many beneficial effects in improving several components of the cardiometabolic risk profile such as intra-abdominal fat accumulation, glucose tolerance, blood pressure as well as several parameters of the lipoprotein-lipid profile [8-10]. Therefore, current guidelines recommend regular and moderate regimens of physical activity [11]. However, whether individuals with MS who are physically active have less CHD consequences of MS and therefore a lower CHD risk is currently unknown.

We hypothesized that among people with MS, those who were physically active would have a lower risk of CHD than those who were inactive. We tested this hypothesis among middle-aged men and women enrolled in the EPIC-Norfolk prospective population study.

Methods

Design

The European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) is a prospective population study of 25,663 men and women aged between 45 and 79 years, resident in Norfolk, United Kingdom. Participants were recruited from age–sex registers of general practices in Norfolk as part of the 10-country collaborative EPIC study designed to investigate dietary and other determinants of cancer. The design and methods of the study have been described in detail [12]. In short, at the baseline survey between 1993 and 1997, participants completed a health and lifestyle questionnaire and non-fasting blood was taken by vein puncture. Blood samples were stored at -80C. Patients admitted to the hospital were identified using their unique National Health Service number by data linkage with ENCORE (East Norfolk Health Authority database). All participants were flagged for death certification at the UK Office of National Statistics, ascertaining vital status for the entire cohort. Participants were identified as having CHD during follow-up if they had a hospital admission and/or died with CHD as underlying cause. Death certificates for all decedents were coded by trained nosologists and coronary heart disease was defined as codes 410-414 , both according to the international classification of diseases, 9th revision. These codes enclose the clinical spectrum of CHD; stable angina, unstable angina and myocardial infarction. Previous validation studies in our cohort indicated high specificity for such case ascertainment [13]. The results in this paper were with a follow-up up to 31 March 2007, an average of 10.9 years. The Norwich District Health Authority Ethics Committee approved the study, all participants gave informed consent.

Participants

From the entire EPIC-Norfolk cohort, we selected the participants who had a complete dataset available for anthropometric variables, blood pressure, lipid parameters, HbA1c, and physical activity. Metabolic syndrome was diagnosed if at least three of the following five criteria were present; elevated waist circumference; ≥102 cm for men and ≥88 cm for women., triglycerides ≥1.7 mmol/L, blood pressure ≥130/85 mmHg, HbA1C ≥6% and HDL <1.03 mmol/L for men and <1.3 mmol/L for women [14]. People who reported coronary heart disease or stroke at the baseline visit were excluded. Cases were persons who developed fatal or non-fatal CAD during follow-up.

Measurements

Serum concentrations of total cholesterol, HDL cholesterol and triglycerides were measured in fresh serum samples with the RA1000 (Bayer Diagnostics, Basingstoke, UK) LDL cholesterol concentrations were calculated with the Friedewald formula. Samples were analysed in random order to avoid systemic bias. Researchers and laboratory personnel had no access to identifiable information and could identify samples by number only. A modified definition of the metabolic syndrome was used and HbA1C was measured instead of fasting glucose because HbA1C levels are more stable then glucose levels and blood samples were not withdrawn in the fasting state. HbA1C measurements were performed as previously described [15], in approximately half the cohort due to financial restrictions. The level of physical activity was assessed by a self-reported composite measure of leisure time and work related physical activity. The EPIC physical activity questions refer to activity during the past year. The first question is a four-point, mutually exclusive, ordered category concerning physical activity at work. The second question asks about the amount of time spent in hours per week for summer and winter separately in each of the following activities: walking, cycling, gardening, do-it-yourself, physical exercise and housework. The original description of the EPIC questions suggested calculation of reported energy expenditure in all of the activities reported in question 2 by multiplying reported time by standard energy costs from published compendia [16]. The third question asks whether any of the activities in question 2 were engaged in such that it caused sweating or faster heartbeat and, if so, for how many hours during a typical week. The fourth question asks about stair climbing [17]. The simple classification of self-reported occupational activity and categorisation of time spent in cycling and other physical exercise were combined to form a physical activity index. Individuals were allocated into four categories of increasing physical activity; very inactive, moderately inactive, moderately active and very active [18,19]. This index was validated against repeated individually calibrated heart rate monitoring in 173 individuals over 1 year [20]. Briefly, the volunteers wore a heart rate monitor (Polar Electro, Finland) continuously during the walking hours of the following four days. The energy expenditure data were summed over the day to create an estimate of daytime expenditure. After adjustment for age and sex, the self-reported physical activity index was positively correlated with mean daytime energy expenditure ($r=0.28$, $p<0.001$). The unadjusted ($r=0.44$, $p<0.001$) and adjusted ($r=0.45$, $p<0.001$) were more strongly correlated. [17]

Statistical analysis: Baseline characteristics were compared between participants who did and did not meet the criteria for the metabolic syndrome. We used an independent samples t-test for normally distributed variables; results are expressed as mean ± standard deviation. The Mann-Whitney U test was used for not normally distributed variables like triglycerides; results are expressed as median and interquartile range. Cardiovascular event rates were calculated for men and women with and without the metabolic syndrome, and compared by Chi square statistics. Hazard ratios for the risk of future CHD were calculated using a proportional hazards model. We used an unadjusted regression model, a sex-, age- and smoking adjusted regression model, and a regression model that additionally adjusted for physical activity. Entering both variables and their product into a logistic regression model assessed statistical interaction between physical activity status and MS status. Statistical analyses were performed using SPSS software (version 12.0.1, Chicago, Illinois). A P-value of <0.05 was considered to indicate statistical significance.

Results

A complete dataset was available for a total of 4423 men and 5711 women. This selection did not differ for any of the baseline characteristics from the EPIC-Norfolk participants who were not included in the present analysis. Baseline characteristics of the study participants are reported in table 1. In this study population, 85.2% of men and 83.6% of women with diabetes met the clinical criteria of the MS. Overall, participants with MS were more inactive than participants without MS (very inactive: 37.2% vs. 26.6%, $p<0.001$ in men and 41.5% vs. 24.7%, $p<0.001$ in women). Table 2 shows the prevalence of individual MS criteria and the prevalence of MS. We identified 1665 men and 1722 women who met the criteria for the metabolic syndrome. The prevalence of MS was 37.6% in men and 30.2% in women.

Table 1. Baseline characteristics

	Men			Women		
	No MS	MS		No MS	MS	
	2758	1665		3989	1722	
Age (years)	57 ± 10	61 ± 9	< 0.001	55 ± 9	63 ± 9	< 0.001
Smoking - current	12.4 (343)	11.8 (197)	< 0.001	12.6 (502)	9.8 (168)	0.001
- previous	48.0 (1323)	58.5 (974)		31.3 (1249)	35.1 (605)	
- never	39.6 (1092)	29.7 (494)		56.1 (2238)	55.1 (949)	
Diabetes	0.6 (17)	5.9 (98)	< 0.001	0.3 (11)	3.3 (56)	< 0.001
BMI (kg/m2)	25.4 ± 2.7	28.1 ± 3.4	< 0.001	24.8 ± 3.5	28.9 ± 4.7	< 0.001
Waist circumference (cm)	92 ± 8	101 ± 10	< 0.001	78 ± 8	90 ± 11	< 0.001
SBP (mmHg)	132 ± 16	145 ± 16	< 0.001	127 ± 17	144 ± 17	< 0.001
DBP (mmHg)	82 ± 10	89 ± 10	< 0.001	78 ± 10	87 ± 10	< 0.001
TC (mmol/L)	5.8 ± 1.0	6.3 ± 1.1	< 0.001	6.0 ± 1.1	6.8 ± 1.2	< 0.001
LDL-C (mmol/L)	3.8 ± 0.9	4.0 ± 1.0	< 0.001	3.8 ± 1.0	4.3 ± 1.1	< 0.001
HDL-C (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	0.04	1.6 ± 0.4	1.5 ± 0.4	< 0.001
Triglycerides (mmol/L)	1.4 (1.1-1.9)	2.2 (1.8-2.8)	< 0.001	1.1 (0.9-1.5)	2.0 (1.6-2.6)	< 0.001
Very inactive	26.6 (733)	37.2 (620)	< 0.001	24.7 (985)	41.5 (715)	< 0.001
Moderately inactive	24.7 (682)	21.7 (361)		33.3 (1330)	29.0 (499)	
Moderately active	24.8 (684)	20.7 (344)		25.0 (996)	18.5 (319)	
Very active	23.9 (659)	20.4 (340)		17.0 (678)	11.0 (189)	

Data are presented as mean ± standard deviation, percentage (number) or median (interquartile range). BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, TC = total cholesterol, LDL-C= low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol.

Table 2. Prevalence of metabolic syndrome (MS) parameters.

	Men	Women
	4423	5711
Metabolic syndrome ≥ 3 criteria	37.6 (1665)	30.2 (1722)
Elevated waist circumference	24.4 (1080)	25.2 (1438)
Low HDL-C	69.8 (3086)	78.6 (4488)
Hypertension	69.0 (3050)	57.3 (3272)
Hypertriglyceridemia	48.2 (2130)	30.9 (1766)
HbA1c > 6%	11.9 (527)	10.1 (579)

Data are presented as percentage (number). HDL-C = high-density lipoprotein cholesterol, HbA1C = Haemoglobin A_{1C}. Cut-off values for elevated waist circumference were ≥102 cm for men and ≥88 cm for women; for triglycerides ≥1.7 mmol/L for blood pressure ≥130/85 mmHg, for HbA1C ≥6%; and for HDL ≤1.03 mmol/L (men) or ≤1.3 mmol/L (women).

A total of 858 participants had a CHD event during follow-up: 548 men and 310 women. CHD event rates were 12.4% among men and 5.4% among women. Event rates for men with MS and without MS were 17.4% and 9.4% respectively ($p<0.001$). The incidence of CHD events during 10.9 years of follow-up was 10.2% among women with MS versus 3.4% among women without MS ($p<0.001$). The hazard ratios for the risk of future CHD among men with MS, adjusted for age and smoking was; 1.52 (95%CI 1.29-1.81) (Table 3). Additional adjustment for physical activity did not attenuate this hazard ratio further; 1.51 (95%CI 1.27-1.79). In women with MS, the hazard ratio for future CHD risk, adjusted for age and smoking was 1.76 (95% CI 1.39-2.23). After additional adjustment for physical activity the hazard ratio was 1.74 (95%CI 1.38-2.21). For mortality, similar patterns were observed: for men, the HR adjusted for age and smoking was 1.25 (95%CI 1.06-1.49) and 1.23 (95%CI 1.04-1.46) after adjusting for physical activity. For women, the respective HR was 1.35 (95%CI 1.10-1.66) and 1.31 (95%CI 1.06-1.61).

Table 3. Risk for future coronary heart disease and mortality in men and women with the metabolic syndrome

	Men with MS	Women with MS
Coronary heart disease		
Unadjusted	1.95 (1.65-2.31)	3.17 (2.53-3.97)
Adjusted for age, smoking	1.52 (1.29-1.81)	1.76 (1.39-2.23)
Adjusted for age, smoking, physical activity	1.51 (1.27-1.79)	1.74 (1.38-2.21)
Mortality		
Unadjusted	1.84 (1.55-2.17)	2.46 (2.02-3.00)
Adjusted for age, smoking	1.25 (1.06-1.49)	1.35 (1.10-1.66)
Adjusted for age, smoking, physical activity	1.23 (1.04-1.46)	1.31 (1.06-1.61)

Hazard ratio (95% CI) for men and women with the metabolic syndrome, compared to those without the metabolic syndrome. Total number of events for coronary heart disease: n=548 for men, n=310 for women. Total number of events for mortality: n=546 for men, n= 392 for women.

Table 4 shows the CHD event rates for EPIC-Norfolk participants with and without MS, in subgroups defined by other cardiovascular risk factors. In all subgroups, the number of CHD events was higher in participants with MS than those without MS.

Figure 1 shows the CHD event rates in men and women with and without MS classified on the basis of their physical activity levels. There was a downward trend in CHD event rates in both men ($p<0.001$) and women ($p<0.005$) with MS with increasing levels of physical activity: CHD event rate was 21.8% (very inactive), 18.0% (moderately inactive), 14.8% (moderately active) and 11.5% (very active) in men with MS. For women with MS, the respective event rates were 12.4%, 10.6%, 7.5% and 5.3%. There was statistical evidence for effect modification by physical activity on the association between MS and CHD risk ($p=0.1$ for men, $p=0.06$ for women, $p=0.006$ for sexes combined).

Table 4. Coronary heart disease event rates by cardiovascular risk factors and metabolic status

Total	Men without MS 2758	Men with MS 1665		Women without MS 3989	Women with MS 1722	
Smoking - current	12.0 (41/343)	19.8 (39/197)	< 0.001	5.4 (27/502)	14.3 (24/168)	< 0.001
- previous	10.3 (136/1323)	19.2 (187/974)	< 0.001	3.1 (39/1249)	10.9 (66/605)	< 0.001
- never	7.4 (81/1092)	13.0 (64/494)	< 0.001	3.0 (68/2238)	9.1 (86/949)	< 0.001
LDL-C >2.5 (mmol/L)	9.8 (250/2558)	17.4 (272/1565)	< 0.001	3.5 (129/3643)	10.4 (172/1658)	< 0.001
HDL-C <1.03/ 1.3 (mmol/L)	12.5 (121/965)	24.5 (91/372)	< 0.001	5.3 (47/884)	11.5 (39/339)	< 0.001
Triglycerides >1.7 (mmol/L)	9.5 (76/802)	17.4 (229/1313)	< 0.001	4.5 (24/537)	11.1 (131/1185)	< 0.001
SBP >130 (mmHg)	12.5 (165/1318)	17.4 (248/1427)	< 0.001	4.9 (71/1454)	9.8 (141/1446)	< 0.001
DBP >85 (mmHg)	12.3 (114/924)	15.8 (170/1079)	0.03	4.4 (38/863)	9.3 (88/944)	< 0.001
HbA1C >=6%	23.1 (12/52)	25.7 (96/374)	0.7	12.3 (9/73)	15.6 (58/372)	0.5

Data are presented as percentage (number of events/ total). LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, SBP = systolic blood pressure, DBP = diastolic blood pressure, HbA1C = Haemoglobin A_{1C}.

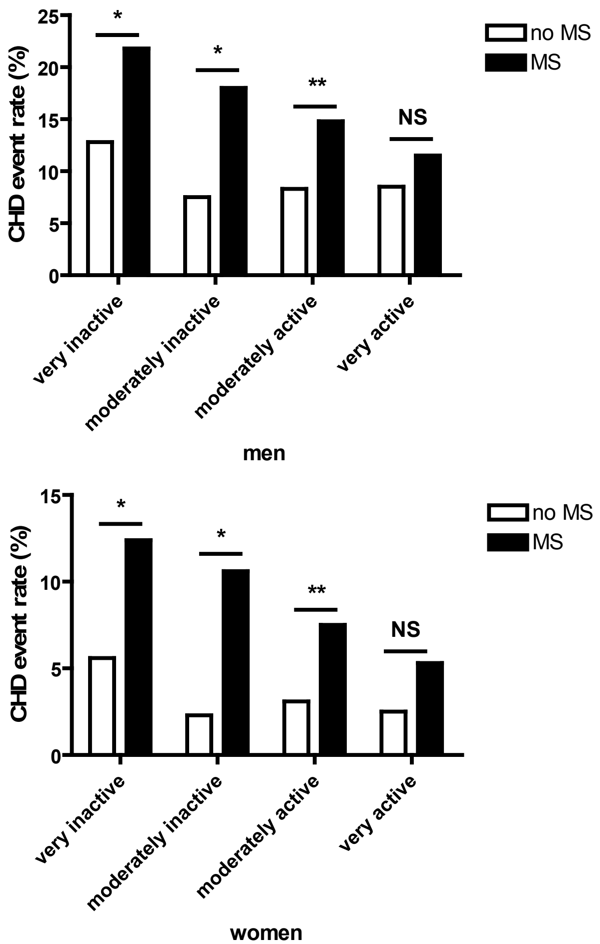

Figure 1. Regular physical activity is associated with a substantial decrease of CHD risk in people with the metabolic syndrome. There was a downward trend in CHD event rates in men with MS: CHD event rate was 21.8% (very inactive), 18.0% (moderately inactive), 14.8% (moderately active) and 11.5% (very active) (p for trend <0.001). This effect was also seen in women with MS, the respective event rates were 12.4%, 10.6%, 7.5% and 5.3% (p for trend <0.005). (** = p<0.001, ** = p=0.001*, so significantly different from participants without the metabolic syndrome)

Discussion

We observed that MS was highly prevalent in the EPIC-Norfolk cohort, a study population representative of a typical Western population, as 37.6% of men and 30.2% of women fulfilled at least three of the five criteria for MS. Men and women with MS had a higher risk of CHD as well as mortality than those without MS. This increased risk associated with the MS was substantially lower among people who were physically active. Also, there was no longer a significant difference in CHD event rate between men and women with MS who were active compared to men and women without MS who were inactive. Altogether, these results suggest that physical activity may attenuate cardiovascular risk in men and women with the metabolic syndrome.

Additional analysis of the EPIC-Norfolk results show a clear dose response relation between PA and the effect of the MS. Current guidelines recommend that people should engage in at least 30 minutes of moderate to intense exercise during most days of the week to stay healthy and prevent CHD [11]. These guidelines suggest that PA becomes beneficial after a certain threshold level is reached. However, the gliding scale of PA level and CHD event rate shown in figure 1 indicates that every other level of PA below this threshold is still an improvement to no PA at all.
Studies investigating the direct effect of exercise training on hard cardiovascular outcomes are scarce and therefore available guidelines are for the greater part based on convincing indirect evidence. For instance, observational studies have shown associations between physical activity levels and various cardiovascular risk factors including the metabolic syndrome, insulin sensitivity and diabetes mellitus [21-23]. Physical activity has also been shown to be associated with a reduced risk of cardiovascular and total mortality [24-27]. This association was explained to a large extent by established risk factors [28]. Interestingly, the Women's Health Study showed that the risk of coronary heart disease associated with elevated body mass index was considerably lower among people with higher physical activity levels [29]. In another study by Sassen et al it was described that PA was inversely associated with the clustering of cardiovascular risk factors associated with the MS. The main characteristic of PA determining the effect on cardiovascular disease being PA intensity and more specific hours performed at high intensity levels [30]. These observations are all consistent with our observations in the EPIC-Norfolk cohort. In addition, several intervention studies have shown that various combinations of lifestyle changes, which usually incorporate increasing physical activity, reduce estimated cardiovascular risk [31,32]. In an analysis of the US Diabetes Prevention Program, lifestyle intervention reduced the incidence of the MS by 41% [33]. In this same study, it was also shown that lifestyle intervention improved the cardiovascular risk factor status of the participants, including hypertension, triglyceride levels, HDL and LDL, without finding a difference in CVD event rate after three years [34].

Limitations

When interpreting the results of the present study, several aspects have to be taken into account. We used a questionnaire that was designed to provide an ordered categorical index of the amount of daily activity during work and leisure time. The reliability of the EPIC physical questions has been reported in a subpopulation of EPIC and the validity demonstrated in a population comparable to EPIC-Norfolk, using repeated objective measurement of cardio-respiratory fitness and individually calibrated heart rate monitoring to measure free-living energy expenditure [20]. The use of a simple ordered index of physical activity introduces the potential for misclassification but such measurement error is likely to be non-differential with respect to the outcome of this study and will, therefore, have the effect of under-estimating (rather than exaggerating) the magnitude of the association between activity and cardiovascular risk. The ascertainment of CHD events through death certification and hospital admission data could theoretically result in true events being missed or alternatively to the false identification of events that are not truly related to coronary heart disease. However, recent validation studies in this cohort ascertain high specificity of these events [13]. The sensitivity of the ascertainment approach is currently unknown, but the impact of missing true events would be to underestimate the CHD incidence and to reduce the power to observe true associations.

In summary, in a cohort representative of a typical European population, we show that men and women with MS have an increased risk of future CHD. Although being physically active did not fully compensate for the increased CHD risk associated with the MS, regular physical activity was associated with a substantially decreased CHD risk in people with the MS. These findings suggest that interventions aiming at increasing physical activity and targeting the specific components of the metabolic syndrome are likely to decrease CHD risk in individuals with the metabolic syndrome.

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Appendix

Interpretation of the physical activity index groups

Label	Description
Very inactive	Sedentary job and no recreational activity
Moderately inactive	Sedentary job with <0.5h recreational activity per day or standing job with no recreational activity per day
Moderately active	Sedentary job with 0.5-1.0h recreational activity per day or standing job with 0.5h recreational activity per day or Physical job with no recreational activity per day
Very active	Sedentary job with >1.0h recreational activity per day or standing job with >0.5h recreational activity per day or physical job with at least some recreational activity or heavy manual job

EPIC physical activity questions

1. We would like to know the type and amount of physical activity involved in your work. Please tick what best corresponds to your present activities from the following four possibilities:

- Sedentary occupation _______
  You spend most of your time sitting (such as in an office)

- *or* Standing occupation ______
  You spend most of your time standing or walking. However, your work does not require intense physical effort (e.g. shop assistant, hairdresser, guard, etc.)

- *or* Physical work ______
  This involves some physical effort including handling of heavy objects and use of tools (e.g. plumber, cleaner, nurse, sports instructor, electrician, carpenter, etc.)

- *or* Heavy manual work ______
  This involves very vigorous physical activity including handling of very heavy objects (e.g. docker, miner, bricklayer, construction worker, etc.)

2. In a typical week during the past 12 months, how many hours did you spend on each of the following activities? (Put '0' if none)

- Walking, including walking to work, shopping and leisure
  in summer ______ hours per week
  in winter ______ hours per week

- Cycling, including cycling to work and during leisure time
  in summer ______ hours per week
  in winter ______ hours per week

- Gardening
  in summer ______ hours per week
  in winter ______ hours per week

- Housework such as cleaning, washing, cooking, childcare
  ______ hours per week

- Do-it-yourself
  ______ hours per week

- Other physical exercise such as keep fit, aerobics, swimming, jogging
  in summer ______ hours per week
  in winter ______ hours per week

3. In a typical week during the past year did you practise any of these activities vigorously enough to cause sweating or a faster heartbeat?

Yes ___ No ___ Don't know____

- If yes, for how many hours per week in total did you practise such vigorous physical activity? (Put '0' if none)

______hours per week

4. In a typical day during the past 12 months, how many floors of stairs did you climb up? (Put '0' if none)

______floors per day

The table and questionnaire in the appendix were adapted from: Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, Public Health Nutrition:2003; 6(4), 407–413