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Inflammatory biomarkers, physical activity, waist circumference, and risk of future coronary heart disease in healthy men and women

Jamal S. Rana[1,2†], Benoit J. Arsenault[3,4†], Jean-Pierre Després[3,5], Mélanie Côté[3,4], Philippa J. Talmud[6], Ewa Ninio[7], J. Wouter Jukema[8], Nicholas J. Wareham[9], John J.P. Kastelein[2], Kay-Tee Khaw[10], and S. Matthijs Boekholdt[2,11*]

[1]Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [2]Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands; [3]Québec Heart Institute Hôpital, Laval Research Centre, Québec, Canada; [4]Department of Anatomy and Physiology, Faculty of Medicine, Université Laval, Québec, Canada; [5]Division of Kinesiology, Faculty of Medicine, Université Laval, Québec, Canada; [6]Division of Cardiovascular Genetics, Royal Free and University College Medical School, London, UK; [7]INSERM UMRS525 (EN); UPMC Université de Paris 06 and Faculté de Médecine Pierre et Marie Curie, Paris, France; [8]Department of Cardiology, Leiden University Medical Center, The Netherlands; [9]Medical Research Council Epidemiology Unit, Cambridge, UK; [10]Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge, UK; and [11]Department of Cardiology, Academic Medical Center, PO Box 22660, 1100 DD Amsterdam, The Netherlands

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Aims The aim of this study was to determine the contribution of physical activity and abdominal obesity to the variation in inflammatory biomarkers and incident coronary heart disease (CHD) in a European population.

Methods and results In a prospective case–control study nested in the European Prospective Investigation into Cancer and Nutrition-Norfolk cohort, we examined the associations between circulating levels or activity of C-reactive protein, myeloperoxidase (MPO), secretory phospholipase A2 (sPLA2), lipoprotein-associated phospholipase A2 (Lp-PLA2), fibrinogen, adiponectin, waist circumference, physical activity, and CHD risk over a 10-year period among healthy men and women (45–79 years of age). A total of 1002 cases who developed fatal or non-fatal CHD were matched to 1859 controls on the basis of age, sex, and enrolment period. Circulating levels of C-reactive protein, sPLA2 (women only), fibrinogen, and adiponectin were linearly associated with increasing waist circumference and decreasing physical activity levels. After adjusting for waist circumference, physical activity, smoking, diabetes, systolic blood pressure, low-density lipoprotein and high-density lipoprotein cholesterol levels, and further adjusted for hormone replacement therapy in women, C-reactive protein, MPO (men only), sPLA2, fibrinogen, but not Lp-PLA2 and adiponectin were associated with an increased CHD risk.

Conclusion Inactive participants with an elevated waist circumference were characterized by deteriorated levels of inflammatory markers. However, several inflammatory markers were associated with an increased CHD risk, independent of underlying CHD risk factors such as waist circumference and physical activity levels.

Keywords Waist circumference • Physical activity • Inflammation • Coronary heart disease

Introduction

More than half of the recent decline in Europe and US coronary heart disease (CHD) mortality rates may be attributable to reductions in major cardiovascular risk factors.[1,2] However, this progress is partially offset by an increase in the prevalence of obesity and related complications.[1,3] Abdominal obesity and physical inactivity are recognized cardiovascular risk factors;[4] although they are interrelated, studies have reported that their associations with CHD risk and all-cause mortality are independent of one another.[5,6]

Abdominal obesity is considered a strong CHD risk factor, independent of body weight.[7] Abdominal obesity, which can be estimated by the measurement of waist circumference, is also

† These authors contributed equally to the manuscript.

* Corresponding author. Tel: +31 20 566 6612, Fax: +31 20 566 9343, Email: s.m.boekholdt@amc.uva.nl

known to be associated with low-grade inflammation.[8] Physical inactivity is also strongly associated with CHD risk and with elevated concentrations of inflammatory markers.[9] However, the respective contributions of abdominal obesity and physical inactivity to the variation in plasma levels of inflammatory markers are not yet established. Although inflammatory markers are strongly associated with an increased risk of CHD,[10] it is unclear to what extent these relationships can be explained by concomitant variations in abdominal obesity and physical inactivity.

We therefore sought to evaluate the associations between abdominal obesity, physical inactivity, and a panel of relevant inflammatory markers including C-reactive protein, myeloperoxidase (MPO), secretory phospholipase A2 (sPLA2), fibrinogen, and adiponectin levels as well as lipoprotein-associated phospholipase A2 (Lp-PLA2) activity. We also wanted to investigate whether the relationship between increased waist circumference and physical inactivity could be explained by inflammatory markers. These sex-specific analyses were conducted in a prospective case–control study among apparently healthy men and women, representative of a contemporary western population.

Methods

Study sample

We conducted a nested case–control study among participants of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk. EPIC-Norfolk is a prospective population study of 25 663 men and women aged 45–79 years residing in Norfolk, UK, who completed a baseline questionnaire survey and attended a clinic visit.[11] Participants were recruited from age and sex registers of general practices in Norfolk as part of the ten-country collaborative EPIC, which was designed to investigate dietary and other determinants of cancer. Additional data were obtained in EPIC-Norfolk, so that determinants of other diseases such as CHD could also be assessed.

The design and methods of EPIC-Norfolk are described in detail elsewhere.[11] In short, eligible participants were recruited by mail. At the baseline survey between 1993 and 1997, participants completed a detailed health and lifestyle questionnaire. All participants were flagged for death certification at the UK Office of National Statistics, and vital status was ascertained for the entire cohort. In addition, hospitalized participants were identified by using their unique National Health Service number through data linkage with the East Norfolk Health Authority database, which identifies all hospital contacts throughout England and Wales for residents of Norfolk. Coronary heart disease was defined as codes 410–414 of the International Classification of Diseases Ninth Revision. Participants were identified as having CHD during follow-up if they had a hospital admission or died with CHD as an underlying cause. Previous validation studies in our cohort indicate high specificity for such case ascertainment.[12] The study was approved by the Norwich District Health Authority Ethics Committee, and all participants gave signed informed consent.

Follow-up and outcome events

We have described this nested case–control study previously.[12,13] We excluded all participants who reported a history of heart attack or stroke or use of lipid-lowering drugs at the baseline clinic visit. Cases were participants who developed fatal or non-fatal CHD during follow-up until November 2003 (mean follow-up, 10 years). A total of 1138 cases were identified. These cases were matched to 2237 controls that were healthy at baseline and remained free of any cardiovascular disease during follow-up. Whenever possible, two controls were matched to each case by age (within 5 years), sex, and time of enrolment period (within 3 months). We identified two controls for 1099 cases and one control only for the remaining 39 cases. We excluded participants with missing data for either smoking, low-density lipoprotein (LDL) or high-density lipoprotein (HDL) cholesterol levels, triglyceride levels, diabetes status, waist circumference, or physical activity and subsequently, we excluded unmatched individuals. A total of 1002 cases and 1859 matched controls were included in the present analyses.

At the baseline survey, participants completed a detailed health and lifestyle questionnaire, and additional data were collected by trained nurses at a clinic visit. Habitual physical activity was assessed using two questions referring to activity during the past year. The first question asked about physical activity at work and the second about the amount of time spent in hours per week in activities: cycling and leisure time physical activities such as jogging or swimming, in winter and summer separately. A simple physical activity index was devised to allocate individuals to four categories of usual increasing physical activity: inactive, moderately inactive, moderately active, and active. This index was validated against heart rate monitoring in 173 individuals over 1 year.[14]

Biochemical analyses

Serum concentrations of total cholesterol, HDL cholesterol, and triglycerides were measured in fresh serum samples with RA1000 (Bayer Diagnostics, Basingstoke, UK), and LDL cholesterol concentrations were calculated with the Friedewald formula. Plasma concentrations of C-reactive protein were measured on thawed frozen plasma from cases and controls. Measurements for MPO,[12] sPLA2,[13] and fibrinogen[15] have been detailed previously. Lipoprotein-associated phospholipase A2 activity was measured, in duplicate, from EDTA plasma stored at −80°C by the trichloroacetic acid precipitation procedure in 96-well plates, as described previously.[16] Adiponectin concentrations were determined by an enzyme-linked immunosorbent assay (B-Bridge International, Inc., San Jose, CA, USA). Samples were analysed in random in order to avoid systemic bias. Researchers and laboratory personnel had no access to identifiable information and could identify samples by number only.

Statistical methods

Because concentrations of triglycerides, C-reactive protein, and adiponectin had a skewed distribution, values were log-transformed before statistical analyses. Untransformed values are shown in the tables. Owing to low prevalence of active and moderately active participants in the case–control study, participants in those categories were pooled into one category, leaving three categories of physical activity of which the most active one was used as reference. Waist circumference was categorized into sex-specific tertiles based on the distribution among controls. Baseline characteristics were compared between cases and controls using a mixed effect model or conditional logistic regression where appropriate. Mean concentrations of inflammatory markers are shown in men and women per category of physical activity sex-specific tertiles of waist circumference. The sex-specific relationship between waist circumference and inflammatory markers was assessed by Spearman's rank correlations. Conditional logistic regression analysis was used to calculate odds ratios (ORs) and corresponding 95% confidence intervals as an estimate of the relative risk of CHD. Odds ratios were calculated per one increase in standard deviation of inflammatory marker and waist circumference and per one

category decrease in physical activity levels. For waist circumference and physical activity, analyses were performed using three regression models. The first model took into account either waist circumference (for the analyses by the physical activity categories) or physical activity levels (for the analyses by waist circumference tertiles), as well as smoking, diabetes, systolic blood pressure, and LDL and HDL cholesterol levels and further adjusted for hormone replacement therapy in women. In the second model, adjustments for the six inflammatory markers were performed. The third model additionally adjusted for the first two models combined. For inflammatory markers, we adjusted for waist circumference, physical activity levels, smoking, diabetes, systolic blood pressure, and LDL and HDL cholesterol levels and further adjusted for hormone replacement therapy in women. All tests were two-sided. However, adjustment for multiple testing was not performed [SPSS software (version 10.1; Chicago, IL, USA)]. A *P*-value of less than 0.05 was considered significant.

Results

A total of 1002 participants (646 men and 356 women) without history of cardiovascular disease at the baseline visit who eventually developed CHD during follow-up were matched to 1859 controls. The matching procedure ensured that sex and age distribution was similar between cases and controls (*Table 1*). Cases were more likely to smoke, have diabetes, be physically inactive, and have an elevated waist circumference. In addition, cases had a higher blood pressure and more detrimental cholesterol indices. Overall, median levels of the inflammatory markers were higher in cases than in controls. Adiponectin was lower in cases than in controls.

Table 2 shows mean levels of inflammatory markers in men and women (cases and controls) classified into tertiles of waist circumference and physical activity categories. Among men and women, C-reactive protein levels increased linearly with decreasing physical activity category within each waist tertile; within each physical activity category, C-reactive protein levels increased positively with waist tertiles. Myeloperoxidase levels were not associated with waist or activity categories among men. However, there was a positive association between MPO levels and waist among inactive and moderately inactive women. Levels of sPLA2 were neither associated with waist nor activity levels in men, whereas

Table 1 Baseline characteristics of cases and controls in men and women

Number of participants	Men		Women	
	Cases 646	Controls 1188	Cases 356	Controls 671
Age (years)	65 ± 8	65 ± 8	66 ± 7	66 ± 7
Smoking				
Current	15.8 (102)	8.4 (100)*	15.2 (54)	8.2 (55)*
Former	59.3 (383)	59.5 (707)	38.5 (137)	36.4 (244)
Never	24.9 (161)	32.1 (381)*	46.3 (165)	55.4 (372)*
Usual physical activity				
Active or moderately active	36.5 (236)	44.4 (527)*	22.2 (79)	31.9 (214)*
Moderately inactive	24.0 (155)	25.3 (301)	28.9 (103)	32.0 (215)*
Inactive	39.5 (255)	30.3 (360)*	48.9 (174)	36.1 (242)*
Diabetes	6.7 (43)	2.0 (24)*	5.3 (19)	0.9 (6)*
BMI (kg/m^2)	27.2 ± 3.5	26.2 ± 3.0*	27.4 ± 4.5	26.2 ± 3.8*
Waist circumference (cm)	98 ± 10	96 ± 9*	87 ± 11	83 ± 10*
Systolic blood pressure (mmHg)	144 ± 19	140 ± 18*	143 ± 19	138 ± 19*
Diastolic blood pressure (mmHg)	87 ± 12	85 ± 11*	85 ± 12	82 ± 11*
Total cholesterol (mmol/L)	6.3 ± 1.1	6.0 ± 1.1*	6.8 ± 1.3	6.6 ± 1.1*
LDL cholesterol (mmol/L)	4.2 ± 1.0	4.0 ± 1.0*	4.5 ± 1.1	4.3 ± 1.1*
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.2 ± 0.3*	1.4 ± 0.4	1.6 ± 0.4*
Triglycerides (mmol/L)	1.9 (1.4–2.7)	1.7 (1.2–2.3)*	1.8 (1.3–2.4)	1.5 (1.1–2.1)*
C-reactive protein (mg/dL)	2.1 (1.0–4.5)	1.4 (0.7–2.9)*	2.6 (1.1–5.9)	1.6 (0.7–3.4)*
Myeloperoxidase (pmol/L)	849 ± 762	729 ± 582*	739 ± 621	660 ± 5.4*
sPLA2 (ng/mL)	10.7 ± 8.6	9.3 ± 7.4*	15.6 ± 12.6	13.0 ± 9.1*
Lp-PLA2 activity (nmol/min/mL)	55.4 ± 17.7	52.9 ± 15.5*	49.9 ± 14.8	46.8 ± 14.9*
Fibrinogen (g/L)	3.1 ± 0.8	3.0 ± 0.7*	3.3 ± 0.8	3.1 ± 0.7*
Adiponectin (μg/mL)	7.7 (5.8–10.6)	8.3 (6.2–11.2)*	11.4 (8.2–15.6)	12.4 (9.1–16.8)*

BMI, body mass index; sPLA2, secretory phospholipase A2; Lp-PLA2, lipoprotein-associated phospholipase A2. Data are presented as mean (± SD), % (*n*), or median (interquartile range).
*There is a statistically significant (<0.05) difference between cases and controls.

Table 2 Levels of circulating inflammatory markers of men and women classified on the basis of tertiles of waist circumference and physical activity levels in EPIC-Norfolk

	Active or moderately active	Moderately inactive	Inactive	*P*-value for linear trend
Men				
Number of participants	763	456	615	
C-reactive protein (mg/dL)				
Waist <91 cm	0.9 (0.5–2.0)	1.1 (0.5–2.5)	1.4 (0.7–2.9)	0.002
Waist 91–98 cm	1.3 (0.7–2.9)	1.7 (0.7–3.4)	1.7 (0.8–3.9)	0.02
Waist ≥98 cm	1.9 (1.0–3.5)	2.0 (1.0–4.2)	2.5 (1.3–6.0)	<0.001
P-value for linear trend	<0.001	<0.001	<0.001	
MPO (pmol/L)				
Waist <91 cm	744 ± 574	734 ± 554	829 ± 806	0.2
Waist 91–98 cm	703 ± 633	826 ± 992	732 ± 506	0.7
Waist ≥98 cm	779 ± 621	729 ± 621	859 ± 674	0.1
P-value for linear trend	0.5	0.8	0.4	
sPLA2 (ng/mL)				
Waist <91 cm	10.2 ± 10.6	9.1 ± 5.9	10.5 ± 9.2	0.8
Waist 91–98 cm	9.1 ± 6.4	9.8 ± 6.8	9.5 ± 6.8	0.5
Waist ≥98 cm	9.4 ± 7.1	9.8 ± 7.8	10.7 ± 8.6	0.05
P-value for linear trend	0.3	0.4	0.5	
Lp-PLA2 (nmol/min/mL)				
Waist <91 cm	51.2 ± 15.5	53.6 ± 15.6	54.2 ± 19.2	0.1
Waist 91–98 cm	54.4 ± 15.5	53.0 ± 16.2	55.1 ± 19.9	0.7
Waist ≥98 cm	54.4 ± 15.4	53.5 ± 15.2	54.2 ± 16.0	0.8
P-value for linear trend	0.03	1.0	0.9	
Fibrinogen (g/L)				
Waist <91 cm	2.8 ± 0.7	2.9 ± 0.8	3.0 ± 0.9	0.02
Waist 91–98 cm	2.9 ± 0.8	3.0 ± 0.8	3.2 ± 0.8	0.002
Waist ≥98 cm	3.0 ± 0.8	3.1 ± 0.7	3.2 ± 0.7	0.004
P-value for linear trend	0.02	0.09	0.1	
Adiponectin (μg/mL)				
Waist <91 cm	8.5 (6.3–11.8)	8.3 (6.2–10.9)	9.5 (7.0–13.0)	0.05
Waist 91–98 cm	8.2 (6.5–11.2)	8.2 (5.2–11.7)	9.0 (6.6–12.1)	0.3
Waist ≥98 cm	7.7 (5.6–10.1)	8.0 (5.7–10.4)	7.4 (5.5–9.9)	0.3
P-value for linear trend	0.02	0.1	<0.001	
Women				
Number of participants	293	318	416	
C-reactive protein (mg/dL)				
Waist <76 cm	0.7 (0.3–1.3)	1.0 (0.4–2.3)	1.2 (0.6–2.7)	0.01
Waist 76–85 cm	1.4 (0.7–3.1)	1.3 (0.7–2.5)	1.8 (0.9–3.6)	0.1
Waist ≥85 cm	2.5 (1.2–5.7)	2.7 (1.2–6.8)	3.3 (1.9–6.8)	0.01
P-value for linear trend	<0.001	<0.001	<0.001	
MPO (pmol/L)				
Waist <76 cm	634 ± 463	562 ± 259	621 ± 409	0.8
Waist 76–85 cm	702 ± 522	667 ± 535	634 ± 587	0.3
Waist ≥85 cm	694 ± 464	742 ± 637	770 ± 630	0.3
P-value for linear trend	0.4	0.04	0.03	
sPLA2 (ng/mL)				
Waist <76 cm	11.8 ± 10.9	13.2 ± 8.4	11.8 ± 8.5	0.9

Continued

Table 2 *Continued*

	Active or moderately active	Moderately inactive	Inactive	*P*-value for linear trend
Waist 76–85 cm	13.1 ± 8.8	12.3 ± 6.3	13.3 ± 10.3	0.8
Waist ≥85 cm	13.8 ± 9.8	15.2 ± 11.1	16.7 ± 13.5	0.048
P-value for linear trend	0.2	0.049	0.001	
Lp-PLA2 (nmol/min/mL)				
Waist <76 cm	43.5 ± 14.1	45.7 ± 16.6	48.0 ± 15.4	0.07
Waist 76–85 cm	45.5 ± 12.7	48.8 ± 12.6	48.5 ± 14.9	0.08
Waist ≥85 cm	48.8 ± 15.1	47.6 ± 14.5	50.3 ± 16.6	0.5
P-value for linear trend	0.007	0.6	0.2	
Fibrinogen (g/L)				
Waist <76 cm	2.9 ± 0.7	2.9 ± 0.8	3.2 ± 0.6	0.005
Waist 76–85 cm	3.2 ± 0.7	3.1 ± 0.7	3.3 ± 0.7	0.2
Waist ≥85 cm	3.2 ± 0.7	3.2 ± 0.7	3.4 ± 0.8	0.02
P-value for linear trend	0.009	0.02	0.08	
Adiponectin (μg/mL)				
Waist <76 cm	13.5 (10.4–18.9)	14.0 (9.8–18.8)	14.6 (10.6–18.8)	0.5
Waist 76–85 cm	11.7 (8.7–16.4)	11.8 (9.3–16.3)	13.6 (9.9–17.5)	0.06
Waist ≥85 cm	11.4 (8.3–15.3)	11.0 (7.8–13.6)	11.4 (8.0–14.9)	0.7
P-value for linear trend	0.02	0.007	<0.001	

Data are presented as mean ± standard deviation or median (interquartile range). MPO, myeloperoxidase; sPLA2, secretory phospholipase A2; Lp-PLA2, lipoprotein-associated phospholipase A2.

Table 3 Spearman correlation coefficients for inflammatory markers and adiposity indices among controls

	C-reactive protein	MPO	sPLA2	LpPLA2	Fibrinogen	Adiponectin	Waist circumference	BMI
Men								
C-reactive protein	—							
MPO	0.24*	—						
sPLA2	0.23*	0.12*	—					
LpPLA2	0.06**	−0.01	0.01	—				
Fibrinogen	0.46*	0.15*	0.17*	0.04	—			
Adiponectin	−0.12	−0.06**	0.03	−0.03	−0.07	—		
Waist circumference	0.25*	0.03	0.02	0.06**	0.13*	−0.15*	—	
BMI	0.24*	0.003	0.05	0.08**	0.13*	−0.15*	0.80*	—
Women								
C-reactive protein	—							
MPO	0.19*	—						
sPLA2	0.30*	0.07	—					
LpPLA2	−0.001	−0.03	0.004	—				
Fibrinogen	0.4*	0.09**	0.14	−0.003	—			
Adiponectin	−0.18	−0.08**	−0.06	−0.05	−0.05	—		
Waist circumference	0.39*	0.07	0.16	0.07	0.13*	−0.22*	—	
BMI	0.43*	0.06	0.16	0.01	0.15*	−0.21*	0.80*	

BMI, body mass index; MPO, myeloperoxidase; sPLA2, secretory phospholipase A2; Lp-PLA2, lipoprotein-associated phospholipase A2.
*There is statistically significant difference ($P < 0.01$).
**There is statistically significant difference ($P < 0.05$).

Table 4 Odds ratio for future coronary heart disease associated with one standard deviation of waist circumference or one decrease in physical activity category in men and women

	Men		Women	
	Odds ratio for future CHD (95% CI)	*P*-value	Odds ratio for future CHD (95% CI)	*P*-value
Waist circumference (unadjusted)	1.35 (1.22–1.50)	<0.001	1.41 (1.23–1.61)	<0.001
Waist circumference[1]	1.26 (1.12–1.41)	<0.001	1.25 (1.07–1.46)	0.004
Waist circumference[2]	1.32 (1.19–1.48)	<0.001	1.27 (1.09–1.48)	0.002
Waist circumference[3]	1.27 (1.13–1.43)	<0.001	1.16 (0.98–1.36)	0.08
Physical inactivity category (unadjusted)	1.20 (1.09–1.32)	<0.001	1.36 (1.18–1.57)	<0.001
Physical inactivity category[4]	1.11 (1.01–1.23)	0.03	1.26 (1.08–1.47)	0.004
Physical inactivity category[2]	1.16 (1.05–1.28)	0.003	1.29 (1.11–1.51)	0.001
Physical inactivity category[5]	1.10 (0.99–1.21)	0.08	1.22 (1.04–1.43)	0.01

Model 1 is adjusted for physical activity, smoking, diabetes, systolic blood pressure, and low-density and high-density lipoprotein cholesterol levels and further adjusted for hormone replacement therapy in women.
Model 2 is adjusted for the six inflammatory markers.
Model 3 is model 1 plus model 2.
Model 4 is model 1, except that physical activity was substituted by waist circumference.
Model 5 is model 4 plus model 2.

Table 5 Odds ratio for future coronary heart disease associated with one standard deviation increase in plasma inflammatory marker levels in men and women

	Men		Women	
	Odds ratio for future CHD (95% CI)	*P*-value	Odds ratio for future CHD (95% CI)	*P*-value
C-reactive protein	1.13 (1.01–1.26)	0.03	1.18 (1.02–1.36)	0.03
MPO	1.17 (1.06–1.30)	0.002	1.10 (0.96–1.26)	0.2
sPLA2	1.31 (1.05–1.64)	0.02	1.37 (1.12–1.67)	0.002
Lp-PLA2	1.02 (0.97–1.08)	0.4	1.04 (0.92–1.17)	0.6
Fibrinogen	1.15 (1.03–1.28)	0.02	1.23 (1.05–1.44)	0.009
Adiponectin	1.02 (0.91–1.14)	0.7	1.01 (0.86–1.18)	0.9

Odds ratios are adjusted for waist circumference, physical activity, smoking, diabetes, systolic blood pressure, and low-density and high-density lipoprotein cholesterol levels and further adjusted for hormone replacement therapy in women.

sPLA2 levels were substantially higher among inactive women who were characterized by an increased waist circumference. Lipoprotein-associated phospholipase A2 activity was associated with increasing waist circumference among active men and women, but not in other physical activity categories. Fibrinogen levels were associated with physical activity levels and waist circumference categories in most subgroups among both men and women. Finally, increasing waist circumference tertiles were associated with a decrease in adiponectin levels among subgroups of physical activity among both men and women. Adiponectin levels did not vary across physical activity categories.

Table 3 shows the Spearman correlation coefficients for inflammatory markers as well as waist circumference and body mass index among controls. In both sexes, waist circumference and body mass index appeared to be positively associated with the variations of plasma C-reactive protein and negatively associated with plasma adiponectin levels. Waist circumference and body mass index were also moderately associated with fibrinogen levels.

The ORs for future CHD associated with variations in waist circumference and physical activity categories are shown in *Table 4*. One increase of standard deviation unit was associated with a 35% increased CHD risk in men and a 41% increased CHD risk in women. In men and women, adjusting for traditional CHD risk factors such as physical activity, smoking, diabetes, systolic blood pressure, and LDL and HDL cholesterol levels (model 1) and adjusting for inflammatory markers (model 2) slightly attenuated CHD risk associated with an increased waist circumference. *Table 4* also shows that one decrease in physical activity category was associated with a 20% increased CHD risk in men and a 36% increased CHD risk in women. Adjusting for traditional CHD risk factors including waist circumference, smoking, diabetes, systolic blood pressure, and LDL and HDL cholesterol levels (model 1) and adjusting for inflammatory markers (model 2) also attenuated CHD risks associated with physical inactivity.

Table 5 shows the adjusted ORs for future CHD associated with one standard deviation increase in plasma inflammatory marker

levels in men and women. In both men and women, plasma levels of sPLA2 appeared to be the inflammatory marker that was more strongly associated with CHD risk. C-reactive protein, fibrinogen, and MPO (men only) also appeared to independently predict CHD risk. We also found that Lp-PLA2 activity and adiponectin levels were not associated with CHD risks after adjusting for waist circumference, physical activity, smoking, diabetes, systolic blood pressure, and LDL and HDL cholesterol levels and hormone replacement therapy in women.

Discussion

In this prospective, population-based case–control study, we found that circulating levels of several inflammatory markers such as C-reactive protein, sPLA2, fibrinogen, and adiponectin were linearly associated with physical inactivity and increasing waist circumference, whereas plasma levels of MPO and Lp-PLA2 activity did not appear to be associated with abdominal obesity or physical activity levels. In this study, both waist circumference and physical activity levels were found to be two strong and independent CHD risk predictors, even after controlling for several well-established CHD risk factors and emerging CHD risk markers associated with low-grade inflammation. Conversely, we found that several inflammatory markers were independently associated with CHD risk. Indeed, after adjusting for waist circumference, physical activity levels, smoking, diabetes, systolic blood pressure, LDL and HDL cholesterol levels and for hormone replacement therapy in women, C-reactive protein, MPO (men only), sPLA2, fibrinogen, but not Lp-PLA2 and adiponectin, were associated with an increased CHD risk.

Abdominal obesity, physical activity, inflammation, and coronary heart disease risk

These findings provide evidence for an important role for low-grade inflammation in predicting CHD risk associated with physical inactivity and abdominal obesity. We also bring solid prospective evidence to observational studies that have been conducted in the past, such as the one by Church *et al.*[17] who have shown that leukocyte count and plasma levels of fibrinogen were inversely associated with fitness and positively with body mass index in men. Recently, Mora *et al.*[18] showed that high body mass index and physical inactivity were related to adverse cardiovascular biomarker levels among women. Limitations of these studies include their cross-sectional design and the impossibility to explore these findings in the context of CHD risk. In addition, these studies were performed in either men[17] or women,[18] explored a limited number of inflammatory markers, and did not discriminate between overall and abdominal obesity. However, other studies have shown conflicting results with regard to the association between physical activity and inflammation.[19,20]

The INTERHEART study[4] suggested that, based on attributable fractions of disease, more than 90% of myocardial infarction could be explained by nine conventional risk factors including an elevated waist-to-hip ratio and physical inactivity, thereby leaving a very small proportion of events to be explained by emerging risk factors/markers such as those included in the present analyses. Under this assumption, one could argue that inflammatory markers might not represent clinically useful CHD risk factors, improving risk prediction and/or stratification. However, although 90% of the CHD events could be explained by conventional risk factors, it has been suggested that the residual risk associated with emerging risk factors could be higher than 10%.[21] This observation combined with recent studies that have shown that inflammatory markers could be useful for CHD risk prediction and stratification points towards a potential role for inflammatory markers in CHD risk management.[22] Previously, C-reactive protein,[10] fibrinogen,[23] MPO,[12] sPLA2,[13] Lp-PLA2,[24] and adiponectin[25] have been shown to be associated with increased risk of CHD. However, to the best of our knowledge, this study is the first ever to explore the association of such novel inflammatory markers and CHD risk in the context of abdominal obesity and physical inactivity.

Several intervention studies have shown that exercise might reduce plasma levels of pro-inflammatory cytokines and induce the expression of antioxidant and anti-inflammatory mediators in the vascular wall, which may directly inhibit the development of atherosclerosis.[26] Adipose tissue located in intra-abdominal or visceral cavities is likely to be infiltrated by macrophage, which is an important cause of the inflammatory state associated with abdominal obesity and the metabolic syndrome. Under these pathophysiological circumstances, the pro-inflammatory effects of cytokines target intracellular signalling pathways such as nuclear factor-κB and c-Jun N-terminal kinase, which upon activation causes local and peripheral insulin resistance.[27] Moreover, interventions targeting excess body weight by increasing physical activity have shown to provide beneficial impact on circulating inflammatory markers.[28]

Limitations

A number of aspects of our study warrant further discussion. Strengths of our study include the large number of participants and the fact that they were recruited from an unrestricted and homogeneous population. In addition, we excluded people who had previously experienced myocardial infarction or stroke, thus limiting the impact of such events on the physical activity level. Also, we studied a composite measure of leisure time and work-related physical activity. Such a combined measure of exposure may be more appropriate than leisure time physical activity alone, as used in numerous other studies. However, participants were categorized according to their self-reported physical activity habits. Measurement errors in self-reported physical activity are inevitable, and random misclassification may have underestimated the association of physical activity with risk of CHD. Nevertheless, this is unlikely to affect the analyses stratified according to physical activity levels substantially. The current study used a physical activity index that has been validated previously using heart rate monitoring over 1 year and indicated good reproducibility and validity about daily energy expenditure.[14] We used waist circumference to estimate abdominal obesity, although waist reflects both subcutaneous abdominal adipose tissue and intra-abdominal adipose tissue volumes.[29] We have chosen waist circumference as a measurement of abdominal adiposity, because it is the most

practical and more applicable in clinical practice.[30,31] Finally, CHD events were not validated by an independent outcome committee. However, validation studies have shown that the outcome definition has high specificity for case ascertainment.[7]

Clinical implications

We believe that the results of the present study could have major clinical implications. First, by showing that both abdominal obesity and physical inactivity are strong and independent CHD risk factors, we underline the importance of physical activity and other possible lifestyle behaviours that are associated with low abdominal obesity levels for the primary prevention of CHD. Because elevated plasma concentrations of certain inflammatory markers appear to be the consequence of increased waist circumference and decreased physical activity levels, such lifestyle interventions could reduce CHD risk by targeting an important source of low-grade inflammation. In contrast, as elevated plasma levels of inflammatory markers are associated with excess risk of CHD, independent of abdominal obesity and physical inactivity, our results support the notion that inflammation might represent a potential target of therapy. In a recent trial[32] performed among apparently healthy individuals with elevated high-sensitivity C-reactive protein levels, statin use significantly reduced the incidence of major cardiovascular events. Another study showed that lowering inflammation could result in improvements in plaque composition.[33]

Conclusions

In conclusion, results of the present study suggest that waist circumference and physical inactivity are strong CHD risk predictors in both men and women from this European cohort. Although inactive individuals with an elevated waistline appeared to have higher plasma levels of specific inflammatory markers, the study shows that the relationship between abdominal obesity and CHD risk or the relationship between physical inactivity and CHD risk cannot be entirely explained by concomitant variation in inflammation markers. However, several inflammatory markers appear to contribute to an increased CHD risk beyond what can be explained by abdominal obesity and physical inactivity.

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