**Supplementary Materials**

**Physical activity attenuates but does not eliminate coronary heart disease risk amongst adults with risk factors: EPIC-CVD case-cohort study**

Melony C Fortuin-de Smidt1, Maquins Odhiambo Sewe1, Camille Lassale2,3, Elisabete Weiderpass4, Jonas Andersson5, José María Huerta6,7, Ulf Ekelund8,9, Krasimira Aleksandrova10,11, Tammy YN Tong12, Christina C Dahm13, Anne Tjønneland14,15, Cecilie Kyrø14, Karen Steindorf16, Matthias B Schulze17,18, Verena Katzke19, Carlotta Sacerdote20, Claudia Agnoli21, Giovanna Masala22, Rosario Tumino23, Salvatore Panico24, Jolanda MA Boer25, N Charlotte Onland-Moret26, GC Wanda Wendel-Vos25, Yvonne T van der Schouw26, Kristin Benjaminsen Borch27, Antonio Agudo28,29, Dafina Petrova30,31,32, María-Dolores Chirlaque33,34, Moreno-Iribas Conchi35,36, Pilar Amiano7,37,38, Olle Melander39,40, Alicia K Heath41, Dagfinn Aune41,42,43,44, Nita G Forouhi45, Claudia Langenberg45,46, Soren Brage45, Elio Riboli41, Nicholas J Wareham45, John Danesh47,48,49,50,51, Adam S Butterworth47,48,49,50, Patrik Wennberg1

**Affiliations**

1Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

2Cardiovascular epidemiology and genetics, Hospital del Mar Research Institute (IMIM), Barcelona, Spain

3CIBER of Pathophysiology of Obesity and Nutrition (CIBEROBN), Instituto de Salud Carlos III, 28029 Madrid, Spain

4International Agency for Research on Cancer, Lyon, France

5Department of Public Health and Clinical Medicine, Skellefteå Research Unit, Umeå University, Sweden

6Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain

7CIBER Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, 28029 Madrid, Spain

8Department of Sports Medicine, Norwegian School of Sport Science, Oslo, Norway

9Department of Chronic Diseases and Ageing, Norwegian Institute of Public Health, Oslo, Norway

10Department Epidemiological Methods and Etiological Research, Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany

11Faculty of Human and Health Sciences, University of Bremen, Bremen, Germany

12Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

13Department of Public Health, Aarhus University, Denmark

14Danish Cancer Society Research Center, Copenhagen, Denmark

15Department of Public Health, University of Copenhagen, Copenhagen, Denmark

16Division of Physical Activity, Prevention and Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany

17Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany

18Institute of Nutritional Science, University of Potsdam, Potsdam, Germany

19Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

20Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital, Turiny, Italy

21Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Italy

22Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence Italy

23Hyblean Association for Epidemiological Research, AIRE-ONLUS, Ragusa, Italy

24Dipartimento di medicina clinica e chirurgia, Federico II University, Naples, Italy

25National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

26Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

27Department of Community Medicine, UiT, The Arctic University of Norway, Tromsø, Norway

28Unit of Nutrition and Cancer, Catalan Institute of Oncology - ICO, L'Hospitalet de Llobregat, Spain

29Nutrition and Cancer Group; Epidemiology, Public Health, Cancer Prevention and Palliative Care Program; Bellvitge Biomedical Research Institute - IDIBELL, L'Hospitalet de Llobregat, Spain

30Escuela Andaluza de Salud Pública (EASP), 18011 Granada, Spain

31Instituto de Investigación Biosanitaria ibs.GRANADA, 18012 Granada, Spain

32Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), 28029 Madrid, Spain

33Department of Epidemiology, Regional Health Council, IMIB-Arrixaca, Murcia University, Murcia, Spain

34CIBER in Epidemiology and Public Health (CIBERESP), Madrid, Spain

35Navarra Public Health Institute, IdiSNA, Pamplona, Spain

36Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Pamplona, Spain

37Ministry of Health of the Basque Government, Sub Directorate for Public Health and Addictions of Gipuzkoa, San Sebastian, Spain

38Biodonostia Health Research Institute, Epidemiology of Chronic and Communicable Diseases Group, San Sebastián, Spain

39Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden

40Department of Emergency and Internal Medicine, Skåne University Hospital, Malmö, Sweden

41Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom

42Department of Nutrition, Bjørknes University College, Oslo, Norway

43Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway

44Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

45MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom

46Computational Medicine, Berlin Institute of Health, Charité-University Medicine Berlin, Berlin, Germany

47British Heart Foundation Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom

48National Institute for Health Research Blood and Transplant Research Unit in Donor Health and Genomics, University of Cambridge, Cambridge, United Kingdom

49British Heart Foundation Centre of Research Excellence, University of Cambridge, Cambridge, United Kingdom

50Health Data Research UK Cambridge, Wellcome Genome Campus and University of Cambridge, Cambridge, United Kingdom

51Department of Human Genetics, Wellcome Sanger Institute, Hinxton, United Kingdom

**Tables**

**Supplementary Table S1.** Comparison of participants included in the complete case analysis and those excluded due to missing values in the sub-cohort and amongst those with CHD events outside the sub-cohort

**Supplemental Table S2** Characteristics of CHD cases outside the sub-cohort (N=8,393) stratified by physical activity and sex

**Supplementary Table S3**. Sensitivity analysis: Hazard ratio for coronary heart disease (CHD) across physical activity levels amongst participants, excluding those with a BMI <18.5kg/m2, with CHD risk factors defined by body mass index (BMI), total cholesterol, hypertension (clinically and/or history), history of diabetes and smoking status and with those without the specific risk factor and inactive as the reference group (Ref).

**Figures**

**Supplementary Figure S1.** Sensitivity analysis:Estimates of coronary heart disease (CHD) across physical activity levels amongst participants with CHD risk factors defined by body mass index (BMI), non-HDL cholesterol, history of diabetes, hypertension (clinically and/or history) and smoking status and with those without the risk factor and inactive as the reference group (REF). The model for each risk factor was adjusted for age at baseline, alcohol consumption, educational level, fruit intake, vegetable intake, the other risk factors and stratified by sex and centre.

**Supplementary Figure S2.** Sensitivity analysis: Estimates of coronary heart disease (CHD) across physical activity levels amongst men with CHD risk factors defined by body mass index (BMI), total cholesterol, history of diabetes, hypertension (clinically and/or history) and smoking status and with those without the risk factor and inactive as the reference group (REF). The model for each risk factor was adjusted for age at baseline, alcohol consumption, educational level, fruit intake, vegetable intake, the other risk factors, and stratified by centre.

**Supplementary Figure S3.** Sensitivity analysis: Estimates of coronary heart disease (CHD) across physical activity levels amongst women with CHD risk factors defined by body mass index (BMI), total cholesterol, history of diabetes, hypertension (clinically and/or history) and smoking status and with those without the risk factor and inactive as the reference group (REF). The model for each risk factor was adjusted for age at baseline, alcohol consumption, educational level, fruit intake, vegetable intake, the other risk factors and stratified by centre.

**Supplemental Table S1**. Comparison of included and excluded participants from the case-cohort study by location in or outside the sub-cohort

|  |  |  |  |
| --- | --- | --- | --- |
|  | Included | Excludeda | P valueb |
| *Sub-cohort n (%)* | 14,663(89.6) | 1,701(10.4) |  |
| Age (years)c | 52.1±9.1 | 54.5±9.0 | <0.001 |
| Follow-up (years)d | 12.8(3.5) | 13.1(3.8) | <0.001 |
| Sex n (%) |   |   | <0.001 |
|  Men (n=6,163) | 5,436(37.1) | 727(42.7) |  |
|  Women (n=10,201) | 9,227(62.9) | 974(57.3) |  |
| Educational level n (%) |   |   | <0.001 |
|  No schooling (n=1,290) | 1,248(8.5) | 42(3.0) |  |
|  Primary (n=5,373) | 4,848(33.1) | 525(37.6) |  |
|  Secondary (n=2,452) | 2,265(15.4) | 187(13.4) |  |
|  Vocational/University(n=6,945) | 6,302(43.0) | 643(46.0) |  |
| Cambridge physical activity index n (%) |   |   | <0.001 |
|  Inactive (n=3,743) | 3,362(22.9) | 381(26.8) |  |
|  Moderately inactive (n=5,485) | 4,987(34.0) | 498(35.1) |  |
|  Moderately active (n=36,46) | 3,342(22.8) | 304(21.4) |  |
|  Active (n=3,209) | 2,972(20.3) | 237(16.7) |  |
| Alcohol consumption n (%) |   |   | <0.001 |
|  None (n=2,713) | 2,438(16.6) | 275(16.6) |  |
|  1 to ≤5 g/day (n=4,917) | 4,394(30.0) | 523(31.5) |  |
|  >5 to ≤10 g/day (n=2,341) | 2,055(14.0) | 286(17.2) |  |
|  >10 to ≤40 g/day (n=4,956) | 4,480(30.6) | 476(28.7) |  |
|  >40 g/day (n=1,396) | 1,296(8.8) | 100(6.0) |  |
| Fruit (g/day)d | 196.7(217.3) | 175.0(185.9) | <0.001 |
| Vegetables (g/day)d | 157.0(140.6) | 154.7(137.3) | 0.084 |
| Body mass index category n (%) |   |   | 0.011 |
|  <25 kg/m2 (n=7,153) | 6,405(43.7) | 748(46.9) |  |
|  25-29.9 kg/m2 (n=6,410) | 5,791(39.5) | 619(38.8) |  |
|  ≥30 kg/m2 (n=2,695) | 2,467(16.8) | 228(14.3) |  |
| Total cholesterol category n (%) |   |   | 0.249 |
|  <5.2 mmol/l (n=4,314) | 4,086(27.9) | 228(25.3) |  |
|  5.2-6.1 mmol/l (n=5,640) | 5,303(36.2) | 337(37.4) |  |
|  ≥6.2 mmol/l (n=5,610) | 5,274(36.0) | 336(37.3) |  |
| Hypertension n (%) |   |   | <0.001 |
|  No (n=10,406) | 9,505(64.8) | 901(59.0) |  |
|  Yes (n=5,783) | 5,158(35.2) | 625(41.0) |  |
| History of diabetes n (%) |   |   | <0.001 |
|  No (n=15,505) | 14,264(97.3) | 1,241(94.4) |  |
|  Yes (n=472) | 399(2.7) | 73(5.6) |  |
| Smoking status n (%) |   |   | <0.001 |
|  Never (n=7,610) | 6,948(47.4) | 662(42.3) |  |
|  Former(n=4,419) | 3,938(26.9) | 481(30.7) |  |
|  Current (n=4,200) | 3,777(25.8) | 423(27.0) |  |
| *CHD cases outside sub-cohort* |  |  |  |
| n (%) | 8,393(64.7) | 4,576(35.3) |  |
| Age (years)c | 58.5±8.2 | 60.4±9.8 | <0.001 |
| Follow-up (years)d | 6.9(5.5) | 7.6(5.8) | <0.001 |
| Sex n (%) |   |   | <0.001 |
|  Men (n=7,577) | 5,087(60.6) | 2,490(54.4) |  |
|  Women (n=5,392) | 3,306(39.4) | 2,086(45.6) |  |
| Educational level n (%) |   |   | <0.001 |
|  No schooling (n=464) | 410(4.9) | 54(1.62) |  |
|  Primary (n=4,920) | 3,551(42.3) | 1,369(39.6) |  |
|  Secondary (n=1,344) | 948(11.3) | 396(11.5) |  |
|  Vocational/University (n=5,122) | 3,484(41.5) | 1,638(47.4) |  |
| Cambridge physical activity index n (%) |   |   | <0.001 |
|  Inactive (n=3,906) | 2,392(28.5) | 1,514(37.4) |  |
|  Moderately inactive (n=3,863) | 2,648(31.6) | 1,215(30.0) |  |
|  Moderately active (n=2,436) | 1,716(20.4) | 720(17.8) |  |
|  Active (n=2,239) | 1,637(19.5) | 602(14.9) |  |
| Alcohol consumption n (%) |   |   | <0.001 |
|  None (n=2,293) | 1,466(17.5) | 827(18.6) |  |
|  1 to ≤5 g/day (n=4,098) | 2,407(28.7) | 1,691(38.0) |  |
|  >5 to ≤10 g/day (n=1,811) | 1,111(13.2) | 700(15.8) |  |
|  >10 to ≤40 g/day (n=3,516) | 2,525(30.1) | 991(22.3) |  |
|  >40 g/day (n=1,111) | 884(10.5) | 227(5.1) |  |
| Fruit (g/day)d | 172.5(195.9) | 171.2(184.8) | 0.271 |
| Vegetables (g/day)d | 151.8(132.5) | 165.1(163.8) | <0.001 |
| Body mass index category n (%) |   |   | <0.001 |
|  <25 kg/m2 (n=4,282) | 2,592(30.9) | 1,690(38.4) |  |
|  25-29.9 kg/m2 (n=5,979) | 4,042(48.2) | 1,937(44.0) |  |
|  ≥30 kg/m2 (n=2,535) | 1,759(21.0) | 776(17.6) |  |
| Total cholesterol category n (%) |   |   | 0.945 |
|  <5.2 mmol/l (n=1,485) | 1,283(15.3) | 202(15.6) |  |
|  5.2-6.1 mmol/l (n=3,081) | 2,670(31.8) | 411(31.8) |  |
|  ≥6.2 mmol/l (n=5,119) | 4,440(52.9) | 679(52.6) |  |
| Hypertension n (%) |   |   | <0.001 |
|  No (n=5,191) | 3,269(38.9) | 1,922(46.9) |  |
|  Yes (n=7,302) | 5,124(61.1) | 2,178(53.1) |  |
| History of diabetes n (%) |   |   | 0.744 |
|  No (n=11,523) | 7,800(92.9) | 3,723(92.8) |  |
|  Yes (n=883) | 593(7.1) | 290(7.2) |  |
| Smoking status n (%) |   |   | <0.001 |
|  Never (n=4,080) | 2,552(30.4) | 1,528(34.9) |  |
|  Former (n=4,313) | 2,751(32.8) | 1,562(35.7) |  |
|  Current (n=4,381) | 3,090(36.8) | 1,291(29.5) |  |

aExcluded due to missing data: Number and percentage of participants (n, %) in the sub-cohort (N=16,364) with missing data per variable: Age (0), sex (0), duration of follow-up (1, 0.01%), body mass index (106, 0.7%), total cholesterol (800, 4.9%), educational level (304, 1.9%), alcohol consumption (41, 0.3%), hypertension (175, 1.1%), history of diabetes (387, 2.4%), physical activity index (281, 1.7%), fruit intake (51, 0.3%), vegetable intake (51, 0.3%). Number and percentage of participants (n) with CHD events outside the sub-cohort (N=12,969) with missing data per variable: Age (0), sex (0), duration of follow-up (0), body mass index (137, 1.3%), total cholesterol (3,284, 25.3%), educational level (1,119, 8.6%), alcohol consumption (140, 1.1%), hypertension (476, 3.7%), history of diabetes (5632, 4.3%), physical activity index (525, 4.1%), fruit intake (470, 3.6%), vegetable intake (470, 3.6%).

bP-values are derived from unpaired t-tests or Mann-Whitney tests for normal and non-normal distributed continuous variables, respectively, or derived from Chi2 tests for categorical variables.

cValues for normally distributed variables are expressed as mean ±standard deviation.

dValues from non-normally distributed variables are expressed as median (interquartile range).

**Supplemental Table S2** Characteristics of CHD cases outside the sub-cohort (N=8,393) stratified by physical activity and sex

|  |  |
| --- | --- |
|  | Physical activity |
|  | Inactive | Moderately inactive | Moderately active | Active | P valuea |
| *Men (n=5,087)* |  |  |  |  |  |
| n (%) | 1,312(25.8) | 1,541(30.3) | 1,127(22.2) | 1,107(21.8) |  |
| Age (years)b | 61.1±8.7 | 57.9±7.8 | 56.2±7.5 | 55.3±7.2 | <0.001 |
| Educational level n (%) |   |   |   |   | 0.012 |
|  No schooling (n=234) | 56(4.3) | 84(5.5) | 58(5.1) | 36(3.3) |  |
|  Primary (n=2,027) | 531(40.5) | 566(36.7) | 451(40.0) | 479(43.3) |  |
|  Secondary (n=561) | 144(11.0) | 189(12.3) | 126(11.2) | 102(9.2) |  |
|  Vocational/University (n=2,265) | 581(44.3) | 702(45.6) | 492(43.7) | 490(44.3) |  |
| Alcohol consumption n (%) |   |   |   |   | <0.001 |
|  None (n=554) | 213(16.2) | 139(9.0) | 101(9.0) | 101(9.1) |  |
|  1 to ≤5 g/day (n=1,157) | 343(26.1) | 348(22.6) | 243(21.6) | 223(20.1) |  |
|  >5 to ≤10 g/day (n=687) | 178(13.6) | 202(13.1) | 152(13.5) | 155(14.0) |  |
|  >10 to ≤40 g/day (n=1,869) | 414(31.6) | 606(39.3) | 426(37.8) | 423(38.2) |  |
|  >40 g/day (n=820) | 164(12.5) | 246(16.0) | 205(18.2) | 205(18.5) |  |
| Fruit (g/day)c | 146.0(192.2) | 150.0(180.5) | 151.7(197.5) | 148.6(184.9) | 0.498 |
| Vegetables (g/day)c | 160.9(156.5) | 149.3(128.9) | 144.1(135.6) | 148.7(124.5) | 0.021 |
| Body mass index n (%) |   |   |   |   | 0.332 |
|  <25 kg/m2 (n=1,365) | 345(26.3) | 423(27.4) | 305(27.1) | 292(26.4) |  |
|  25-29.9 kg/m2 (n=2,701) | 672(51.2) | 823(53.4) | 605(53.7) | 601(54.3) |  |
|  ≥30 kg/m2 (n=1,021) | 295(22.5) | 295(19.1) | 217(19.3) | 214(19.3) |  |
| Total cholesterol n (%) |   |   |   |   | 0.120 |
|  <5.2 mmol/l (n=887) | 222(16.9) | 286(18.6) | 174(15.4) | 205(18.5) |  |
|  5.2-6.1 mmol/l (n=1,742) | 425(32.4) | 527(34.2) | 414(36.7) | 376(34.0) |  |
|  ≥6.0 mmol/l (n=2,458) | 665(50.7) | 728(47.2) | 539(47.8) | 526(47.5) |  |
| Hypertensiond n (%) |   |   |   |   | <0.001 |
|  No (n=2,064) | 463(35.3) | 619(40.2) | 478(42.4) | 504(45.5) |  |
|  Yes (n=3,023) | 849(64.7) | 922(59.8) | 649(57.6) | 603(54.5) |  |
| History of diabetes n (%) |   |   |   |   | <0.001 |
|  No (n=4,731) | 1,186(90.4) | 1,436(93.2) | 1,068(94.8) | 1,041(94.0) |  |
|  Yes (n=356) | 126(9.6) | 105(6.8) | 59(5.2) | 66(6.0) |  |
| Smoking status n (%) |   |   |   |   | 0.664 |
|  Never (n=1,071) | 271(20.7) | 323(21.0) | 245(21.7) | 232(21.0) |  |
|  Former (n=1,927) | 518(39.5) | 594(38.5) | 414(36.7) | 401(36.2) |  |
|  Current (n=2,089) | 523(39.9) | 624(40.5) | 468(41.5) | 474(42.8) |  |
| *Women (n=3,306)* |  |  |  |  |  |
| n (%) | 1,080(32.7) | 1,107(33.5) | 589(17.8) | 530(16.0) |  |
| Age (years)b | 61.4±8.7 | 59.8±7.6 | 58.8±7.3 | 57.1±7.5 | <0.001 |
| Educational level n (%) |   |   |   |   | <0.001 |
|  No schooling (n=176) | 97(9.0) | 59(5.3) | 13(2.2) | 7(1.3) |  |
|  Primary (n=1,524) | 587(54.4) | 481(43.5) | 261(44.3) | 195(36.8) |  |
|  Secondary (n=387) | 107(9.9) | 135(12.2) | 67(11.4) | 78(14.7) |  |
|  Vocational/University (n=1,219) | 289(26.8) | 432(39.0) | 248(42.1) | 250(47.2) |  |
| Alcohol consumption n (%) |   |   |   |   | <0.001 |
|  None (n=912) | 401(37.1) | 289(26.1) | 124(21.1) | 98(18.5) |  |
|  1 to ≤5 g/day (n=1,250) | 402(37.2) | 402(36.3) | 227(38.5) | 219(41.3) |  |
|  >5 to ≤10 g/day (n=424) | 118(10.9) | 148(13.4) | 88(14.9) | 70(13.2) |  |
|  >10 to ≤40 g/day (n=656) | 140(13.0) | 243(22.0) | 142(24.1) | 131(24.7) |  |
|  >40 g/day (n=64) | 19(1.8) | 25(2.3) | 8(1.4) | 12(2.3) |  |
| Fruit (g/day)c | 209.5(213.3) | 210.0(183.2) | 214.3(195.4) | 225.8(189.9) | 0.687 |
| Vegetables (g/day)c | 173.5(159.3) | 154.9(121.1) | 145.8(107.1) | 148.6(88.6) | <0.001 |
| Body mass index n (%) |   |   |   |   | <0.001 |
|  <25 kg/m2 (n=1227) | 318(29.4) | 428(38.7) | 249(42.3) | 232(43.8) |  |
|  25-29.9 kg/m2 (n=1,341) | 450(41.7) | 434(39.2) | 244(41.4) | 213(40.2) |  |
|  ≥30 kg/m2 (n=738) | 312(28.9) | 245(22.1) | 96(16.3) | 85(16.0) |  |
| Total cholesterol n (%) |   |   |   |   | 0.371 |
|  <5.2 mmol/l (n=396) | 123(11.4) | 148(13.4) | 67(11.4) | 58(10.9) |  |
|  5.2-6.1 mmol/l (n=928) | 293(27.1) | 327(29.5) | 159(27.0) | 149(28.1) |  |
|  ≥6.0 mmol/l (n=1,982) | 664(61.5) | 632(57.1) | 363(61.6) | 323(60.9) |  |
| Hypertensiond n (%) |   |   |   |   | <0.001 |
|  No (n=1,205) | 341(31.6) | 414(37.4) | 236(40.1) | 214(40.4) |  |
|  Yes (n=2,101) | 739(68.4) | 693(62.6) | 353(59.9) | 316(59.6) |  |
| History of diabetes n (%) |   |   |   |   | 0.001 |
|  No (n=3,069) | 980(90.7) | 1026(92.7) | 555(94.2) | 508(95.8) |  |
|  Yes (n=237) | 100(9.3) | 81(7.3) | 34(5.8) | 22(4.2) |  |
| Smoking status n (%) |   |   |   |   | <0.001 |
|  Never (n=1,481) | 508(47.0) | 538(48.6) | 244(41.4) | 191(36.0) |  |
|  Former (n=824) | 260(24.1) | 261(23.6) | 148(25.1) | 155(29.2) |  |
|  Current (n=1,001) | 312(28.9) | 308(27.8) | 197(33.4) | 184(34.7) |  |

aP values are derived from a Kruskal Wallis or ANOVA test for continuous variables or from a Chi2 test for categorical variables;

 bValues for normally distributed variables are expressed as mean ±standard deviation;

cValues from non-normally distributed variables are expressed as median (interquartile range);

dHypertension definition is based on medical history and/or clinical measurements.

**Supplementary Table S3**. Sensitivity analysis: Hazard ratio for coronary heart disease across physical activity levels amongst participants, excluding those with a BMI <18.5kg/m2, with CHD risk factors defined by body mass index (BMI), total cholesterol, hypertension (clinically and/or history), history of diabetes and smoking status and with those without the specific risk factor and inactive as the reference group (REF).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Risk factor category | Physical activity level | HRa (95% Cl) | N participants | N cases |
| BMI kg/m2 |  |  |  |  |
| 18.5-24.9 | **Inactive** | **1.0 (REF)** | 1,762 | 675 |
|  | Moderately inactive | 0.91 (0.82-1.01) | 3,010 | 875 |
|  | Moderately active | 0.84 (0.73-0.95) | 2,107 | 574 |
|  | Active | 0.84 (0.74 -0.95) | 1,917 | 545 |
| 25-29.9 | Inactive  | 1.30 (1.18-1.43) | 2,477 | 1,202 |
|  | Moderately inactive | 1.19 (1.03 -1.37) | 3,257 | 1,345 |
|  | Moderately active | 1.09 (0.92-1.28) | 2,138 | 903 |
|  | Active | 1.09 (0.93-1.27) | 1,961 | 861 |
| ≥30 | Inactive  | 1.48 (1.32 -1.65) | 1,461 | 646 |
|  | Moderately inactive | 1.35 (1.16 -1.57) | 1,305 | 579 |
|  | Moderately active | 1.24 (1.04 -1.46) | 764 | 330 |
|  | Active | 1.24 (1.05-1.46) | 696 | 317 |
| Total cholesterol mmol/l |  |  |  |  |
| <5.2  | Inactive  | **1.0 (REF)** | 1,215 | 362 |
|  | Moderately inactive | 0.91 (0.82-1.01) | 1,790 | 452 |
|  | Moderately active | 0.84 (0.73-0.95) | 1,184 | 258 |
|  | Active | 0.84 (0.74 -0.95) | 1,112 | 273 |
| 5.2-6.1 | Inactive  | 1.26 (1.10-1.44) | 1,912 | 754 |
|  | Moderately inactive | 1.15 (0.97 -1.36) | 2,617 | 907 |
|  | Moderately active | 1.05 (0.87-1.27) | 1,799 | 599 |
|  | Active | 1.06 (0.88 -1.26) | 1,572 | 560 |
| ≥6.2 | Inactive  | 1.81 (1.56-2.11) | 2,573 | 1,407 |
|  | Moderately inactive | 1.66 (1.38-1.99) | 3,165 | 1,440 |
|  | Moderately active | 1.51 (1.24-1.85) | 2,026 | 950 |
|  | Active | 1.52 (1.25-1.85) | 1,890 | 890 |
| Hypertension |  |  |  |  |
| No | Inactive | **1.0 (REF)** | 2,864 | 856 |
|  | Moderately inactive | 0.91 (0.82-1.01) | 4,197 | 1,088 |
|  | Moderately active | 0.84 (0.73-0.95) | 2,947 | 751 |
|  | Active | 0.84 (0.74 -0.95) | 2,614 | 747 |
| Yes | Inactive  | 1.80 (1.65-1.96) | 2,836 | 1,667 |
|  | Moderately inactive | 1.65 (1.44-1.89) | 3,375 | 1,711 |
|  | Moderately active | 1.51 (1.29-1.76) | 2,062 | 1,056 |
|  | Active | 1.51 (1.30-1.75) | 1,960 | 976 |
| History of diabetes |  |  |  |  |
| No | Inactive  | **1.0 (REF)** | 5,342 | 2,279 |
|  | Moderately inactive | 0.91 (0.82-1.01) | 7,260 | 2,601 |
|  | Moderately active | 0.84 (0.73-0.95) | 4,833 | 1,703 |
|  | Active | 0.84 (0.74 -0.95) | 4,430 | 1,631 |
| Yes | Inactive  | 2.41 (1.62-3.59) | 358 | 244 |
|  | Moderately inactive | 2.20 (1.46-3.33) | 312 | 198 |
|  | Moderately active | 2.01 (1.32-3.06) | 176 | 104 |
|  | Active | 2.02 (1.33-3.06) | 144 | 92 |
| Smoking status |  |  |  |  |
| Never | Inactive  | **1.0 (REF)** | 2,560 | 833 |
|  | Moderately inactive | 0.91 (0.82-1.01) | 3,240 | 898 |
|  | Moderately active | 0.84 (0.73-0.95) | 1,950 | 509 |
|  | Active | 0.84 (0.74 -0.95) | 1,669 | 443 |
| Former | Inactive  | 1.34 (1.19 -1.50) | 1,455 | 810 |
|  | Moderately inactive | 1.22 (1.05-1.43) | 2,179 | 912 |
|  | Moderately active | 1.12 (0.94-1.33) | 1,528 | 585 |
|  | Active | 1.12 (0.95-1.33) | 1,491 | 587 |
| Current | Inactive  | 2.54 (2.23-2.88) | 1,685 | 880 |
|  | Moderately inactive | 2.32 (1.97-2.74) | 2,153 | 989 |
|  | Moderately active | 2.12 (1.77-2.54) | 1,531 | 713 |
|  | Active | 2.13 (1.78-2.53) | 1,414 | 693 |

aHazard Ratio (HR) and 95% Confidence Intervals (CI) estimated from Prentice-weighted Cox proportional hazard models. The model for each risk factor was adjusted for age at baseline, alcohol consumption, educational level, fruit intake, vegetable intake, and all the other risk factors, stratified by sex and center. HRs were first estimated per center and then combined by multivariate random-effect meta-analysis. Analysis included 22,855 participants, including 8,852 incident CHD cases.

**Supplementary Figure S1.** Sensitivity analysis:Combinedestimates of coronary heart disease (CHD) across physical activity levels amongst participants with CHD risk factors defined by body mass index (BMI), non-HDL cholesterol, history of diabetes, hypertension (clinically and/or history) and smoking status and with those without the risk factor and inactive as the reference group (REF). The model for each risk factor was adjusted for age at baseline, alcohol consumption, educational level, fruit intake, vegetable intake, the other risk factors and stratified by sex and centre. N=23,051, including 8,389 CHD cases



**Supplementary Figure S2.** Sensitivity analysis: Combined estimates of coronary heart disease (CHD) across physical activity levels amongst men with CHD risk factors defined by body mass index (BMI), total cholesterol, history of diabetes, hypertension (clinically and/or history) and smoking status and with those without the risk factor and inactive as the reference group (REF). The model for each risk factor was adjusted for age at baseline, alcohol consumption, educational level, fruit intake, vegetable intake, the other risk factors, and stratified by centre. n=10,523 participants, including 5,408 CHD cases

****

**Supplementary Figure S3.** Sensitivity analysis: Combined estimates of coronary heart disease (CHD) across physical activity levels amongst women with CHD risk factors defined by body mass index (BMI), total cholesterol, history of diabetes, hypertension (clinically and/or history) and smoking status and with those without the risk factor and inactive as the reference group (REF). The model for each risk factor was adjusted for age at baseline, alcohol consumption, educational level, fruit intake, vegetable intake, the other risk factors and stratified by centre. n=12,533 participants, including 3,306 CHD cases

****