

Physical functional health predicts the incidence of coronary heart disease in the European Prospective Investigation into Cancer (EPIC)-Norfolk prospective population based study

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Revision 1: Physical functional health predicts the incidence of coronary heart disease in the European Prospective Investigation into Cancer (EPIC)-Norfolk prospective population based study

Short title: Physical functional health and incident CHD

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Abstract

Background: Little is known about the relationship between physical functional health and long-term risk of coronary heart disease (CHD) independently of known risk factors in a general population.

Methods: Men and women aged 40-79 years at baseline who completed a health and lifestyle questionnaire and attended a health examination during 1993-1997 participating in the European Prospective Investigation into Cancer (EPIC)-Norfolk who were free of myocardial infarction (MI), stroke and cancer were included. Physical functional health was assessed using physical component summary (PCS) scores of SF-36 eighteen months later. The incidence of CHD was ascertained by death certification and hospital record linkage up to March 2008.

Results: A total of 14,222 men and women were included in the study. There were 389 incident CHD (total person years = 126,896 years). People who reported better physical functional health had significantly lower risk of coronary heart disease. Using Cox proportional hazard models adjusting for age, sex, body mass index, cholesterol, systolic blood pressure, smoking, alcohol consumption, physical activity, diabetes, family history of MI, social class, and aspirin usage, men and women who were in the top quartile of SF-36 PCS had half the risk of CHD ((RR=0.46;95%CI:0.32-0.65) compared to the people in the bottom quartile. The relationships remained essentially unchanged after excluding incident CHD within the first 2 years of follow-up (RR=0.48;95%CI:0.33-0.70).

Conclusions: Physical functional health predicts subsequent CHD risk independently of known risk factors in a general population. People with poor physical functional health may benefit from targeted preventive interventions.

Introduction

Coronary heart disease (CHD) remains the number one cause of death in the Western societies and the global burden of cardiovascular disease is expected to rise. In the US alone, each year ~ 1.1 million persons have a myocardial infarction (MI) [1]. Early identification and appropriate management of people who are at risk of developing CHD has huge potential in reducing global burden of cardiovascular diseases.

The Short-Form 36 item questionnaire (SF-36) is a widely used and well validated questionnaire [2] which assesses an individual's self-reported physical and mental functional health. The physical component summary (PCS) score or physical functional health of SF-36 measures an individual's capability to perform physical tasks such as carrying grocery, walking etc. Although it was originally designed to assess the efficacy of treatment/s provided from patients' perspective, recent evidence suggests that physical functional health may also serve as a predictor of objective health outcomes such as mortality [3] and chronic disabling condition such as stroke [4] independently of known risk factors.

In this study we examine the relationship between self-reported physical functional health measured by PCS scores of SF-36 and incidence of coronary heart disease in a large British prospective population based study.

Methods

Study sample

The participants were 14,222 men and women, aged 40-79 years at the baseline, drawn from the Norfolk, UK component of the European Prospective Investigation into Cancer (EPIC-Norfolk). The EPIC-Norfolk is a prospective population-based study, described in detail elsewhere [5]. Briefly, the participants were recruited from age-sex registers of general practices. As virtually 100% of people in the UK are registered with general practitioners through the National Health Service, the age-sex registers form a population-based sampling frame. From the inception of the EPIC-Norfolk cohort, data collection was broadened to enable the examination of a wider range of determinants of chronic diseases including coronary heart disease. The Norfolk cohort was comparable to national population samples with respect to characteristics including anthropometry, blood pressure, and lipids, but with a lower prevalence of current smokers [5]. The Norwich Local Research Ethics Committee approved the study.

There were a total of 30,445 who consented to participate (40% of the eligible general population). The majority (99.6%) are British White Caucasians. After excluding people who did not attend health check (4846), those who did not have SF-36 data (10,910), and prevalent stroke (455), MI (977) and cancer (1642) at baseline, the current report is based on 14,222 participants aged 40-79 years at the baseline. Not all who attended health check provided SF-36 data and vice versa. Comparison between participants who completed the SF-36 and those who did not, showed no material difference, though statistically significantly different due to large numbers

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3 were found for age, sex, body mass index, systolic blood pressure and cholesterol
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5 level (appendix).
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10 **Measurements**

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12 Study participants completed a baseline health and lifestyle questionnaire and
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14 attended a clinic at the study baseline during 1993-1997. Height, weight, and blood
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16 pressure (BP) were measured by trained staff using standardized protocols [6]. Means
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18 of two measures of systolic BP was used. Non-fasting blood samples were taken.
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20 Serum total cholesterol was measured on fresh samples with the RA 1000 (Bayer
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22 Diagnostics, Basingstoke, UK).
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30 Participants were asked “Have you ever smoked as much as one cigarette a day for as
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32 long as a year?” and “Do you smoke cigarettes now?” in the baseline questionnaire
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34 and classified as current or ex-smokers, or those who had never smoked. A four-level
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36 physical activity index (level I = inactive, II = moderately inactive, III = moderately
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38 active, IV = active) was derived from the EPIC validated short physical activity
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40 questionnaire [7]. The detailed description of this physical activity questionnaire had
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42 been previously reported [8][9]. This index was validated against heart rate
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44 monitoring with individual calibration in two independent studies [10][11].
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51 Alcohol consumption derived from the question “How many alcoholic drinks do you
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53 have each week?” with four separate categories of drinks. A unit of alcohol
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55 (approximately 8 g) was defined as a half pint of beer, cider, or lager; a glass of wine;
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57 a single unit of spirits (whisky, gin, brandy, or vodka); or a glass of sherry, port,
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3 vermouth, or liqueurs. Total alcohol consumption was estimated as the total units of
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5 drinks consumed in a week.
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10 At the baseline, they were also asked, “Has a doctor ever told you that you have any
11 of the following?” followed by a list of conditions to obtain baseline prevalent
12 illnesses which included stroke, heart attack, cancer and diabetes. Family history of
13 myocardial infarction was ascertained from the question “Have any of your
14 immediate family had any of the following conditions” which included “heart attack”.
15 Social class was classified according to the Registrar General’s occupation-based
16 classification [12] (I= professionals, II =managerial and technical occupations, III
17 =skilled workers (non-manual and manual), IV= partly skilled workers, V =unskilled
18 manual workers). Social classes I, II, and III non-manual were re-categorised as “non-
19 manual” and III manual, IV and V as “manual” [13]. Aspirin use was ascertained by
20 a question “Have you taken aspirin continuously for 3 months or more?”.
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39 Eighteen months later, the surviving participants were asked to complete by mail a
40 psychosocial questionnaire [14] that included the anglicised version of SF-36 (UK
41 SF-36). This assessment included eight dimensions (subscales) of health: physical
42 functioning, social functioning, role limitation due to physical problems, role
43 limitation due to emotional problems, mental health, energy/vitality, pain and general
44 health perception.
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55 Briefly, scores for each dimension are obtained by summing of scores from individual
56 relevant responses concerned with that particular health dimension. For each health
57 dimension (subscale) the raw scores were transformed into a scale from 0 to 100;
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3 score 0 represents poor health and 100 represents good health for each subscale.
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6 Scoring on the 0 to 100 metric provides with a score that represents the percentage of
7
8 the total possible score that the participant received. This score is computed by: 1)
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10 subtracting the lowest possible raw score from the participant's actual raw score; 2)
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12 dividing this number by the possible raw score range; and 3) multiplying this number
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14 by 100.
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20 Physical Component Summary (PCS) scores were derived according to algorithms
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22 specified by the original developers [2][15]. They were created by aggregating across
23
24 the eight SF-36 subscales after transforming to z-scores and multiplying by their
25
26 respective factor score coefficients and standardised as T-scores with mean 50 and SD
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28 10 [14]. Three scales (Physical Functioning, Role-Physical, and Bodily Pain) correlate
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30 most highly with the physical component and contribute most to the scoring of the
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32 PCS measure.
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40 **Outcome measures**

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42 Complete follow-up of the study sample was achieved using death certification at the
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44 UK Office of National Statistics and hospital record linkage with vital status
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46 ascertained for the whole cohort. Incident cases of coronary heart disease were
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48 identified by the Tenth Revision of the International Classification of Diseases (ICD
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50 10) code I10-I79. The follow-up period commenced from time of completion of the
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52 SF-36 (18 months after baseline) and until date of myocardial infarction or 31st
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54 March 2008 as the end of follow up date.
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Statistical analyses

Statistical analyses were performed using SPSS for Windows Version 14.0 (SPSS Inc., Chicago, Illinois). We used Cox proportional hazards model [16] to determine the overall and sex-specific independent association of physical functional health with incident coronary heart disease adjusting firstly for age (model A); secondly for age, and sex (model B); thirdly age, sex, systolic BP, body mass index (BMI), cholesterol level (model C); fourthly additionally adjusting for lifestyle behaviours including smoking status, alcohol consumption and physical activity (model D); fifthly additionally adjusting for history of diabetes and family history of MI (model E); then including occupational social class (model F) and finally additionally adjusting for prior aspirin use (model G).

To address the reverse causality issue we excluded all those who had CHD within the first two, four and six years of follow-up and constructed further models (models H, I and J) controlling for all of the above mentioned variables (as in model G).

All numerical data were entered as continuous variables and ordinal data as categorical variables. Initial analyses were performed using SF-36 PCS quartile categories. As there was continuous inverse dose-response relationship, the analyses were repeated using every 10 points (approximately 1 SD) increase in SF-36 PCS as the predictor variable. We also explored the association between SF-36 PCS and fatal and non-fatal CHD adjusting for confounders (model G).

Results

After exclusion of participants with prevalent myocardial infarction, stroke and cancer, a total of 14,222 participants aged 40-79 years at the time of study enrolment were included in the current report. There were a total of 389 incident coronary heart disease cases (fatal = 102, 26.2%) during the follow-up (total person years 126,896 years, mean follow-up 8.9 years).

Table 1 shows the sample characteristics by quartiles of SF-36 physical component summary scores. Quartile 1 represents the bottom 25% and quartile 4 represents the top 25%. The corresponding SF-36 PCS scores for quartile 1, 2, 3 & 4 were 5.20-43.50, 43.51-51.00, 51.01-55.10, and 55.11-72.10, respectively. Participants who reported better physical functional health (those in higher quartile) were significantly younger, more likely to be men, had lower body mass index, cholesterol level and systolic blood pressure. The proportion of participants who smoke, those with history of diabetes and family history of MI, and prior aspirin usage were significantly lower in those participants who were in the top quartile compared to the bottom quartile. People in the top quartile are more likely to be physically active and being less likely to be from lower occupational social class background. Weekly alcohol consumption differed statistically significantly between top and bottom quartiles. The average alcohol consumption, however, was well within the recommended weekly limit for UK population. The unadjusted rates for coronary heart disease were 4.5%, 3.0%, 2.1% and 1.2% during the follow up for quartile 1, 2, 3, and 4, respectively.

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3 Table 2 shows the relative risks and their corresponding 95% confidence interval for
4 having a diagnosis of coronary heart disease by quartiles of physical component
5
6 summary scores of SF-36, firstly for all and then for men and women separately. In
7
8 all models the results were consistent. Participants with highest SF-36 PCS scores
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10 (quartile 4) compared to the lowest (quartile 1) had significant relative risk reduction
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12 (54%) for incident CHD during the follow-up (RR 0.46; 95% CI: 0.32-0.65) in the
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14 fully adjusted model controlling for age, sex, body mass index, cholesterol, systolic
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16 blood pressure, smoking, alcohol consumption, physical activity, diabetes, family
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18 history of MI, social class, and aspirin usage (model G & Figure 1). Exclusion of
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20 CHD diagnosed within first two years of follow-up (model H) attenuated the results
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22 only slightly (RR 0.48; 95%CI: 0.33-0.70). Sensitivity analysis after excluding people
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24 with known diabetes as the prevalence of diabetes was hugely different between
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26 physical functional quartiles (2.9% in Q1 and 0.8% in Q4), did not alter the results
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28 (RR 0.46; 95% CI: 0.32-0.66).
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39 Table 3 shows the relative risks reduction and their corresponding 95% confidence
40 interval for having coronary heart disease by every increase in 10 points of SF-36
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42 PCS scores (1 SD equivalent) controlling for age, sex (in sex-combined analyses),
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44 body mass index, cholesterol, systolic blood pressure, smoking status, alcohol
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46 consumption, physical activity, history of diabetes and family history of myocardial
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48 infarction, social class and prior aspirin usage. Every increase in 10 points (1 SD
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50 equivalent) of SF-36 PCS was associated with significant relative risk reduction of
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52 24% (RR 0.76; 95%CI: 0.69-0.84). The relationships between SF-36 PCS and CHD
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54 remained consistent when fatal and non-fatal CHD were examined separately. The RR
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3 were 0.78 and 0.75 for fatal and non-fatal CHD with every increase in 1SD (10
4 points) of SF-36 PCS showing risk reduction of 22% and 25%, respectively (table 3).
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10 Similar to the above findings in table 2, exclusion of CHD diagnosed within first two
11 years of follow-up only attenuated the results slightly and relative risk reduction
12 remained highly significant (RR 0.79; 95% CI: 0.71-0.87). Further models excluding
13 initial four and six years of follow-up (models C & D) showed similar results.
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For Review Only

Discussion

Self-reported physical functional health assessed by SF-36 was inversely related to risk of incident coronary heart disease independently of known risk factors in a general population free of known heart attack, stroke and cancer at the baseline. The strengths of our study include a prospective design, a study population drawn from the community, case ascertainment using objective death certificates and hospital record linkage data and the ability to adjust for known biological, social and lifestyle risks factors for both physical functional health and coronary heart disease.

In constructing SF-36, symptoms and problems that are specific to a particular condition were not included. The comparison with other longer measures such as Sickness Impact Profile and Health Insurance Experiment battery, however, showed that the SF-36 includes eight of the most frequently represented health concepts [15]. The plausible mechanisms by which baseline physical functional health predicts subsequent risk of coronary heart disease is unclear. Future studies should look for plausible explanations of the associations.

The relative risk reduction for every increase in 10 points of SF-36 PCS (1 SD increase) were 21% in men (RR 0.79, 95%CI: 0.70-0.89) and 27% in women (RR 0.73, 95%CI: 0.62-0.87) in the current study. There was some attenuation of relative risk in both men and women after excluding early coronary heart disease (18% and 25%, respectively). Interestingly, these findings are similar to our previous report for the relationship between physical functional health and stroke incidence [4]. This consistent finding of relationship between physical functional health and subsequent

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3 cardiovascular and cerebrovascular conditions raises an interesting hypothesis that
4 maintaining or prevention of decline in physical functional health in ageing
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6 populations may have added benefit in prevention of cardiovascular diseases.
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12 It may be possible to attenuate the decline in physical functional health associated
13 with chronological age. We have shown the relationships between modifiable lifestyle
14 behaviours such as smoking, physical activity, and alcohol consumption and other
15 potential determinants of SF-36 in the EPIC-Norfolk cohort [17][18][19][20]. In this
16 study we also adjusted for these factors and the relationships observed appeared to be
17 independent of these factors. It may be that SF-36, being a health profile measure
18 reflects the overall health status of an individual, and captures subclinical stage of
19 conditions before it can be detected by objective measures such as a diagnosis made
20 based on a blood test result. Poor physical functional health may reflect underlying
21 biological processes such as chronic inflammation which may relate to coronary heart
22 disease. It is also possible that a poor score may reflect psychosocial factors such as
23 stress which may also influence cardiovascular risk. The PCS score of SF-36 may
24 therefore be a potential useful additional marker in assessing coronary heart disease
25 risk. Our findings suggest that inclusion of physical functional health assessment in
26 predicting cardiovascular risk may be a useful approach to identify better people at
27 high risk of future coronary heart disease at the population level in an apparently
28 coronary heart disease free population. However, further studies in different
29 populations are required to replicate these findings.
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Study limitations

Underestimation of incident coronary events results towards the null, i.e. underestimate the magnitude of the association. Using self-reported myocardial infarction to exclude people with prevalent disease may have missed some prevalent CHD cases. Reverse causality is a potential major issue. People who are already ill might be more likely to be physically inactive and change their lifestyle (e.g. smoking habit) as a result of prevalent disease. To address this we excluded those with prevalent myocardial infarction, stroke and cancer at the baseline and also adjusted for other potential indicators of ill health such as blood pressure, cholesterol concentration, body mass index, diabetes mellitus, and aspirin use, and also repeated the analyses excluding people with coronary heart disease diagnosed within the first two years of follow-up. People with angina have been shown to have impaired health related quality of life [21]. However, the exclusion of coronary heart disease incidents occurring within first two years of follow up did not alter the results significantly. The residual confounding with known or unknown factors is always possible.

We used only one measure at one point in time to characterise individuals and did not take into account possible changes in lifestyles or other treatment effects on the variables we examined (e.g. antihypertensive medication or cholesterol lowering therapy during the study period). Nevertheless, random measurement error would probably attenuate any associations observed, so the estimated differences in risk are likely to be larger than those observed.

Because participants had to be willing to provide detailed information and participate in a long-term follow-up, the EPIC-Norfolk had modest participation rate of ~40% of

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3 the eligible population at the baseline despite 100% follow-up rate. However, EPIC-
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5 Norfolk sample is comparable with the other representative National Surveys in UK
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8 with only slight lower prevalence of smokers [5][14]. The potential healthy responder
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10 bias resulting in truncation of sample distribution would probably only attenuate the
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12 findings and very unlikely to change the direction of the study results. We were not
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14 able to examine the relationship between the SF-36 PCS and incident CHD in the
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16 whole cohort. This is due to the fact that SF-36 survey was not completed by all
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18 participants and we also excluded anyone with missing variables which are included
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20 in the current report. Exclusion of these individuals, however, is unlikely to influence
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22 the internal relationship between physical functional health and incidence of coronary
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24 heart disease in the study population.
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32 **Conclusion**

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34 Physical functional health-related quality of life measured as PCS scores of SF-36
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36 predicts subsequent risk of coronary heart disease independently of known risk factors
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38 in a general population without history of ischemic heart disease at the baseline. The
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40 nature of the association between physical functioning and subsequent risk of CHD
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42 needs further exploration. Further studies could perhaps investigate different ethnic
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44 populations to reflect the current situation of increasing number of diverse
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46 populations in the UK. In the interim, regardless of the underlying mechanism, a poor
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48 physical function score may identify men and women in the apparently healthy
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50 general population at increased risk of coronary event independent of classical risk
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52 factors. People with low level of SF-36 PCS may benefit most from targeted
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54 preventive interventions such as management of known risk factors and increase
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56 uptake of positive lifestyle behaviours.
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Competing interests

None

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Ethics Approval

The Norwich Local Research Ethics Committee approved the study. The corresponding address for the Norwich LREC is Clinical Governance Department, Aldwych House, 57 Bethel Street, Norwich.

Contributors

KTK and NJW are principal investigators in EPIC-Norfolk population study. PGS is the principal investigator of EPIC- Norfolk HLEQ programme. RNL is responsible for data management, computing and data linkages. PKM and NWJW conducted the analyses. PKM prepared the draft manuscript and all co-authors contributed in writing of this paper. KTK is the guarantor.

References

[1] American Heart Association. Heart and Stroke Facts: 2000 Statistical Supplement. Dallas, Tex: American Heart Association; 1999.

[2] Ware JE, Kosinski M, Keller S. SF-36 physical and mental health summary scales: a user's manual. Boston, MA, USA: New England Medical Center, The Health Institute; 1994.

[3] Myint PK, Luben RN, Surtees PG, Wainwright NW, Welch AA, Bingham SA, Day NE, Wareham NJ, Khaw KT. Relation between self-reported physical functional health and chronic disease mortality in men and women in the European Prospective Investigation into Cancer (EPIC-Norfolk): a prospective population study. *Ann Epidemiol.* 2006;16:492-500.

[4] Myint PK, Surtees PG, Wainwright NW, Luben RN, Welch AA, Bingham SA, Wareham NJ, Khaw KT. Physical health-related quality of life predicts stroke in the EPIC-Norfolk. *Neurology.* 2007;69:2243-8.

[5] Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, Wareham N. EPIC-Norfolk: Study design and characteristics of the cohort. *Br J Cancer* 1999; 80:95-103.

[6] Lohman T, Roche A, Martorell R. Anthropometric standardization reference manual. Champaign, IL: Human Kinetics Books; 1991.

[7] Khaw KT, Jakes R, Bingham S, Welch A, Luben R, Day N, Wareham N. Work and leisure time physical activity assessed using a simple, pragmatic, validated questionnaire and incident cardiovascular disease and all-cause mortality in men and women: The European Prospective Investigation into Cancer in Norfolk prospective population study. *Int J Epidemiol.* 2006;35:1034-43.

[8] Myint PK, Luben RN, Wareham NJ, Welch AA, Bingham SA, Day NE, Khaw KT. Combined work and leisure physical activity and risk of stroke in men and women in the European prospective investigation into Cancer-Norfolk Prospective Population Study. *Neuroepidemiology.* 2006;27:122-9.

[9] Khaw KT, Wareham N, Bingham S, Welch A, Luben R, Day N. Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. *PLoS Med.* 2008; 5:e12.

[10] Wareham NJ, Jakes RW, Rennie KL, Mitchell J, Hennings S, Day NE. Validity and repeatability of the EPIC-Norfolk Physical Activity Questionnaire. *Int J Epidemiol.* 2002;31:168-74.

[11] Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE. 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 Nutr.* 2003;6:407-13.

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2
3
4
5 [12] Elias P, Halstead K, Prandy K. CASOC: Computer-Assisted Standard
6 Occupational Coding. HMSO: London; 1993.
7

8 [13] Shohaimi S, Luben R, Wareham N, et al. Residential area deprivation predicts
9 smoking habit independently of individual educational level and occupational social
10 class. A cross sectional study in the Norfolk cohort of the European Investigation into
11 Cancer (EPIC- Norfolk). J Epidemiol Community Health 2003; 57: 270-6.
12

13 [14] Surtees PG, Wainwright NWJ, and Khaw, K.T. Obesity, confidant support and
14 functional health: cross-sectional evidence from the EPIC-Norfolk cohort. Int J Obes
15 Relat Metab Disord. 2004; 28: 748-58.
16
17

18 [15] Ware JE, Snow K, Kosinski M, Gandek B. SF-36 Health Survey: Manual and
19 Interpretation Guide. Boston, MA, USA: New England Medical Center, The Health
20 Institute; 1993.
21
22

23 [16] Cox DR. Regression models and life tables. J R Stat Soc B 1972;34:187-220.
24
25

26 [17] Myint PK, Luben RN, Surtees PG, Wainwright NWJ, Welch AA, Bingham SA,
27 Wareham NJ, Day NE, Khaw KT. Respiratory function and self-reported functional
28 health: EPIC-Norfolk population study. Eur Respir J 2005; 26: 494-502.
29

30 [18] Myint PK, Welch AA, Luben RN, Wainwright NWJ., Surtees PG, Bingham SA,
31 Wareham NJ, Smith RD, Harvey IM, Khaw KT. Obesity indices and self-reported
32 functional health in men and women in the EPIC-Norfolk. Obesity 2006;14 : 884-93.
33
34

35 [19] Myint PK, Welch AA, Bingham SA, Luben RN, Surtees PG, Wainwright NWJ,
36 Wareham NJ, Smith RD, Harvey IM, Khaw KT. Fruit and vegetable consumption and
37 self-reported functional health in men and women in the European Prospective
38 Investigation into Cancer-Norfolk (EPIC-Norfolk): a population based cross sectional
39 study. Public Health Nutr 2006; 10, 34-41.
40
41

42 [20] Myint PK, Surtees PG, Wainwright NWJ., Wareham NJ, Bingham SA, Luben
43 RN, Welch AA, Smith RD, Harvey IM, Khaw KT. Modifiable lifestyle behaviors and
44 functional health in the European Prospective Investigation into Cancer (EPIC)-
45 Norfolk population study. Prev Med 2007; 44: 109-16.
46
47

48 [21] Marquis P, Fayol C, Joire JE. Clinical validation of a quality of life questionnaire
49 in angina pectoris patients. Eur Heart J 1995; 16: 1554-60.
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Table 1 sample characteristics of 14,222 men and women by quartile of Short Form-36 Physical Component Summary (PCS)

	Q1	Q2	Q3	Q4	P
	5.20-43.50	43.51-51.00	51.01-55.10	55.11-72.10	
	3555	3586	3558	3523	
Age (years)	61.4 (9.0)	59.0 (8.9)	57.0 (8.6)	54.3 (8.2)	<0.0001
Age* (years)	64.1 (9.0)	61.6 (8.9)	59.6 (8.6)	56.9 (8.2)	<0.0001
Sex					<0.0001
Male	1435 (40.4)	1648 (46.0)	1673 (47.0)	1561 (44.3)	
Female	2120 (59.6)	1938 (54.0)	1885 (53.0)	1962 (55.7)	
BMI (kg/m ²)	27.1 (4.4)	26.4 (3.8)	25.9 (3.5)	25.2 (3.2)	<0.0001
Cholesterol (mmol/L)	6.3 (1.2)	6.2 (1.1)	6.1 (1.1)	6.1 (1.2)	<0.0001
Systolic BP (mmHg)	138 (19)	136 (18)	134 (18)	131 (17)	<0.0001
Smoking					<0.0001
Current	402 (11.3)	366 (10.2)	342 (9.6)	344(9.8)	
Former	1615 (45.4)	1531 (42.7)	1432 (40.2)	1301 (36.9)	
Never-smoked	1538 (43.3)	1689 (47.1)	1784 (50.1)	1878 (53.3)	
Alcohol (units/week)	6.1 (9.1)	7.4 (9.5)	7.5 (9.3)	7.8 (9.3)	<0.0001
Diabetes (yes)	104 (2.9)	75 (2.1)	54 (1.5)	28 (0.8)	<0.0001
Physical activity					<0.0001
Inactive	1301 (36.6)	996 (27.8)	822 (23.1)	652 (18.5)	
Moderately inactive	1012 (28.5)	1074 (29.9)	1080 (30.4)	1031 (29.3)	
Moderately active	706 (19.9)	855 (23.8)	926 (26.0)	943 (26.8)	
Active	536 (15.1)	661 (18.4)	730 (20.5)	897 (25.5)	
Social class					<0.0001
I	193 (5.4)	259 (7.2)	318 (8.9)	309 (8.8)	
II	1201 (33.8)	1323 (36.9)	1437 (40.4)	1472 (41.8)	
III nonmanual	655 (18.4)	626 (17.5)	583 (16.4)	551 (15.6)	
III manual	828 (23.3)	804 (22.4)	697 (19.6)	742 (21.1)	
IV	518 (14.6)	470 (13.1)	419 (11.8)	368 (10.4)	

V	160 (4.5)	104 (2.9)	104 (2.9)	81 (2.3)	
Aspirin use (yes)	432 (12.2)	257 (7.2)	197 (5.5)	105 (3.0)	<0.0001
Family history of MI (yes)	1413 (39.7)	1327 (37.0)	1281 (36.0)	1224 (34.7)	<0.0001
Incidence of CHD (number, crude rate)	163 (4.5)	110 (3.0)	73 (2.1)	43 (1.2)	<0.0001

* Age at the time of completion of SF-36. P values indicate the level of significance between all quartiles.

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Table 2 Relative risk and corresponding 95% confidence intervals for having a coronary heart disease (CHD) by quartiles of physical functional health assessed by quartiles of SF-36 Physical Component Summary (PCS) score in 14,222 men and women of EPIC-Norfolk (1993/1997-2008)

	Q1	Q2	Q3	Q4	p
All (events=389)					
Model A	1.00	0.74 (0.58-0.95)	0.57 (0.43-0.75)	0.41 (0.29-0.57)	<0.0001
Model B	1.00	0.69 (0.54-0.88)	0.51 (0.39-0.67)	0.38 (0.27-0.53)	<0.0001
Model C	1.00	0.70 (0.55-0.89)	0.53 (0.40-0.70)	0.39 (0.28-0.55)	<0.0001
Model D	1.00	0.73 (0.58-0.94)	0.56 (0.42-0.75)	0.42 (0.30-0.60)	<0.0001
Model E	1.00	0.74 (0.58-0.94)	0.57 (0.43-0.76)	0.44 (0.31-0.62)	<0.0001
Model F	1.00	0.74 (0.58-0.95)	0.57 (0.43-0.76)	0.44 (0.31-0.62)	<0.0001
Model G	1.00	0.75 (0.59-0.96)	0.59 (0.45-0.79)	0.46 (0.32-0.65)	<0.0001
Model H (events=339)	1.00	0.86 (0.67-1.12)	0.61 (0.45-0.84)	0.48 (0.33-0.70)	<0.0001
Model I (events=263)	1.00	0.80 (0.59-1.07)	0.57 (0.40-0.80)	0.42 (0.27-0.65)	<0.0001
Model J (events=181)	1.00	0.81 (0.57-1.15)	0.50 (0.33-0.77)	0.38 (0.23-0.65)	<0.0001
Men (events=271)					
Model A	1.00	0.74 (0.55-0.99)	0.59 (0.42-0.81)	0.40 (0.27-0.61)	<0.0001
Model C	1.00	0.75 (0.55-1.00)	0.60 (0.44-0.84)	0.40 (0.27-0.61)	<0.0001
Model D	1.00	0.79 (0.59-1.07)	0.66 (0.47-0.91)	0.44 (0.29-0.67)	0.001
Model E	1.00	0.79 (0.59-1.07)	0.67 (0.48-0.93)	0.46 (0.30-0.69)	0.001
Model F	1.00	0.80 (0.59-1.07)	0.66 (0.48-0.92)	0.45 (0.30-0.69)	0.001
Model G	1.00	0.81 (0.60-1.10)	0.69 (0.49-0.96)	0.48 (0.32-0.72)	0.004
Model H (events=233)	1.00	0.94 (0.68-1.29)	0.74 (0.52-1.06)	0.50 (0.32-0.79)	0.016
Model I (events=178)	1.00	0.77 (0.53-1.11)	0.66 (0.44-0.99)	0.41 (0.24-0.70)	0.008
Model J (events=122)	1.00	0.73 (0.47-1.13)	0.58 (0.35-0.96)	0.38 (0.20-0.71)	0.014
Women (events=118)					
Model A	1.00	0.62 (0.40-0.97)	0.35 (0.19-0.64)	0.33 (0.17-0.65)	<0.0001
Model C	1.00	0.65 (0.42-1.00)	0.37 (0.20-0.68)	0.37 (0.19-0.74)	0.001
Model D	1.00	0.68 (0.44-1.05)	0.39 (0.21-0.73)	0.40 (0.20-0.80)	0.003
Model E	1.00	0.68 (0.44-1.06)	0.40 (0.22-0.74)	0.41 (0.20-0.81)	0.005
Model F	1.00	0.69 (0.44-1.06)	0.40 (0.22-0.75)	0.41 (0.21-0.82)	0.005

Model G	1.00	0.70 (0.45-1.08)	0.41 (0.22-0.76)	0.42 (0.21-0.84)	0.007
Model H (events=106)	1.00	0.79 (0.50-1.24)	0.39 (0.20-0.75)	0.46 (0.23-0.93)	0.015
Model I (events=85)	1.00	0.91 (0.56-1.49)	0.36 (0.16-0.77)	0.45 (0.21-0.99)	0.022
Model J (events=59)	1.00	1.00 (0.56-1.79)	0.31 (0.12-0.81)	0.37 (0.14-1.00)	0.025

Model A: age (age at the time of completion of SF-36) adjusted; Model B: age and sex adjusted (for sex-combined analyses only) Model C: age, sex (for all), body mass index, cholesterol level, and systolic blood pressure adjusted model; Model D: as in model C with additional adjustment of life style behaviours of smoking, alcohol consumption and physical activity; Model E = as in model D with additional adjustment for history of diabetes and family history of MI; Model F: as in model E with additional adjustment for social class; Model G = as in model F plus aspirin use – adjusted; Model H: as in the final model (model G) after exclusion of coronary heart disease occurring within initial 2 years of follow-up; Model I: as in the model G after exclusion of coronary heart disease occurring within first 4 years of follow-up and Model J: as in the model G after exclusion of coronary heart disease occurring within first 6 years of follow-up. For sex-specific analyses, sex (dichotomised) was not included in the model. P values indicate the level of significance between all quartiles.

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Table 3 Relative Risk (95% confidence intervals) of risk of coronary heart disease (CHD) by 10 points (1 SD equivalent) increase in SF-36 Physical Component Summary (PCS) scores in men and women of EPIC-Norfolk

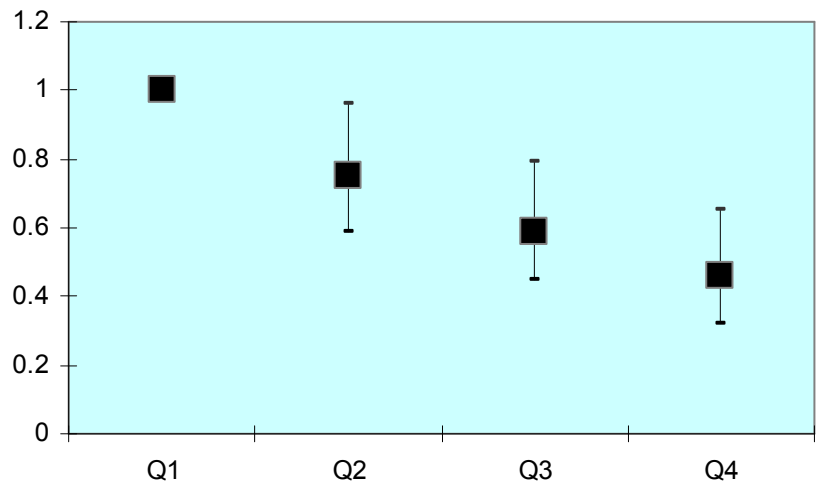
	Relative Risk	95% CI	p
Model A			
All	0.76	0.69-0.84	<0.0001
Men	0.79	0.70-0.89	<0.0001
Women	0.73	0.62-0.87	<0.0001
Fatal events			
All	0.78	0.65-0.94	0.01
Men	0.87	0.67-1.13	0.30
Women	0.70	0.53-0.94	0.016
Non fatal events			
All	0.75	0.67-0.84	<0.0001
Men	0.77	0.67-0.88	<0.0001
Women	0.74	0.60-0.91	0.005
Model B			
All	0.79	0.71-0.87	<0.0001
Men	0.82	0.72-0.93	0.002
Women	0.75	0.62-0.89	0.001
Model C			
All	0.76	0.67-0.85	<0.0001
Men	0.77	0.66-0.89	<0.0001
Women	0.76	0.62-0.92	0.006
Model D			
All	0.73	0.63-0.84	<0.0001
Men	0.75	0.63-0.89	0.001
Women	0.72	0.56-0.91	0.006

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6 In both models adjustments were made for age at the time of completion of SF-36, sex (in sex-combined models only), body mass index,
7 cholesterol, systolic blood pressure, smoking status, alcohol consumption, physical activity, history of diabetes and family history of myocardial
8 infarction, social class and prior aspirin usage. Model A- including all over the whole length of the study follow-up; model B – after exclusion of
9 those who had CHD within first two years of follow-up; model C – after exclusion of those who had CHD within first four years of follow-up;
10 model D – after exclusion of those who had CHD within first six years of follow-up.
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Figure 1 Showing the Relative Risks (95% confidence interval) by quartiles of Short-Form 36 Physical Component Summary (PCS) score in fully adjusted model (model G)



Q1=quartile 1, Q2= quartile 2, Q3= quartile 3, Q4 = quartile 4 of physical functional health

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Figure legend

Figure 1 Showing the Relative Risks (95% confidence interval) by quartiles of Short-Form 36 Physical Component Summary (PCS) score in fully adjusted model (model G)

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Appendix

Table showing characteristics of participants who completed SF-36 questionnaire and those who did not

	SF-36 data available		SF-36 data not available	
	Number	N (%) or Mean (sd)	Number	N (%) or Mean (sd)
	19,535		10,910	
Men		8598 (44.0)		5102 (46.8)
Women		10937 (56.0)		5807 (53.2)
Age*(years)	19,535	58.6 (9.2)	10,909	59.4 (9.8)
BMI (kg/m ²)	17,127	26.3 (3.9)	8,458	26.6 (4.0)
Current smokers		1670 (0.09)		2061 (0.19)