Lifestyle and cardiovascular disease in middle-aged British men: the effect of adjusting for within-person variation

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Aims To examine the effect that within-person variation has on the estimated risk associations between cigarette smoking, physical inactivity, and increased body mass index (BMI) and the development of cardiovascular disease (CVD) in middle-aged British men.

Methods and results In total, 6452 men aged 40–59 with no prior evidence of CVD were followed for major CVD events (fatal/non-fatal myocardial infarction or stroke) and all-cause mortality over 20 years; lifestyle characteristics were ascertained at regular points throughout the study. A major CVD event within the first 20 years was observed in 1194 men (18.5%). Use of baseline assessments of cigarette smoking and physical activity in analyses resulted in underestimation of the associations between average cumulative exposure to these factors and major CVD risk. After correction for within-person variation, major CVD rates were over four times higher for heavy smokers (>/=21 cigarettes/day) compared with never smokers and three times higher for physically inactive men compared with moderately active men. Major CVD risk increased by 6% for each 1 kg/m² increase in usual BMI. If all men had experienced the risk levels of the men who had never regularly smoked cigarettes, were moderately active, and had a BMI of <=20 kg/m² (6% of the population), 66% of the observed major CVD events would have been prevented or postponed (63% before adjustment for within-person variation). Adjustment for a range of other risk factors had little effect on the results. Similar results were obtained for all-cause mortality.

Conclusion Failure to take account of within-person variation can lead to underestimation of the importance of lifestyle characteristics in determining CVD risk. Primary prevention through lifestyle modification has a great preventive potential.

KEYWORDS
Cardiovascular disease; Lifestyle; Risk factors; Within-person variation

Introduction
Observational cohort studies have clearly demonstrated that cigarette smoking, physical inactivity, and increased body mass index (BMI) are associated with increased risks of premature cardiovascular disease (CVD) and death.1-8 The relative effects of these three 'lifestyle' risk factors (as well as their combined effects) on cardiovascular risk are important because they indicate the extent that long-term CVD rates may be reduced through population-wide changes in lifestyle. This is usually calculated by relating 'baseline' measurements of risk factors to subsequent disease (with or without adjustment for other risk factors) in an attempt to identify the nature of the 'aetiological' association, and then multiplying together the individual relative risks to obtain the overall relative risk reduction associated with several aspects of 'healthy living'. However, risk associations derived from baseline measures may not necessarily identify the true aetiological relationship because of within-person variation, a phenomenon well recognized for continuous risk factors.9-11 In addition, multiplying relative risks may overestimate or underestimate true combined relative risk reductions, both because of the use of correlated imprecisely measured baseline measurements in analyses12 and because of possible interactions between the risk factors (which individual studies may be underpowered to detect). Moreover, estimates of relative risk are of little practical relevance in public health terms unless they also take into account the proportion of the population exposed to the 'high-risk' characteristics.

In this paper, we use data from a prospective study of CVD in middle-aged men (the British Regional Heart Study, BRHS) to examine the strength of relationships between three lifestyle risk factors for CVD (cigarette smoking, physical activity, and BMI) and major CVD risk over 20 years in men with no previous evidence of CVD, both before and after

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adjustment for within-person variation in these risk factors. The effects of long-term population-wide changes in lifestyle are subsequently estimated by comparing the CVD risks of never-smoking, physically active, non-overweight men with all remaining men and calculating the proportion of all CVD events attributable to these characteristics. Parallel analyses for all-cause mortality are presented.

Methods

The BRHS is a prospective study of CVD in one general practice in each of 24 British towns. In 1978–80, 7735 men aged 40–59 were recruited into the study. Since the baseline assessment and surviving men have been followed up for all-cause mortality and cardiovascular morbidity, with <1% of participants being lost to follow-up,14 follow-up questionnaires were completed by study participants in 1983–85 (Q5: after 5 years of follow-up), in 1992 (Q92), in 1996 (Q96), and between 1998 and 2000 (Q20: after 20 years of follow-up), providing information on lifestyle risk factor patterns during the follow-up period (study questionnaires are available from the BRHS website: www.ucl.ac.uk/primcare-popsci/brhs). At the baseline and 20 year assessments, questionnaires were nurse administered; training sessions were provided to ensure consistency between the nurses in the way each question was asked.

Assessment of baseline CVD

At the baseline assessment, participants were asked about recall of any doctor diagnosis of myocardial infarction, stroke, or angina and whether they had ever had a history of severe chest pain lasting 30 min or more, which caused them to consult a doctor. Participants also completed a WHO (Rose) angina questionnaire providing evidence of definite or possible angina. Individuals with recall of myocardial infarction, angina, or stroke or with a history of severe chest pain or Rose angina questionnaire providing evidence of definite or possible angina (or any combination of these) were excluded from analyses.

Baseline assessment of lifestyle risk factors

Height without shoes and weight in trousers and socks were measured, to the nearest millimetre and 0.1 kg, respectively, and BMI was calculated as weight in kgs divided by height in metres squared (kg/m²). From the administered questionnaire, men were categorized as current smokers, ex-smokers, or non-smokers; those who smoked less than one cigarette per day were classified as non-smokers (or ex-smokers if they had previously regularly smoked more than one cigarette per day), whereas current smokers were subsequently categorized into three groups depending on the number of cigarettes they smoked each day (1–20, 21–39, or ≥40). Smoking categories were subsequently internally validated against both blood cadmium and cotinine levels.15,16 Physical activity during leisure time was assessed by a number of questions regarding regular walking or cycling, recreational activity, and sporting activity (see questionnaire on the BRHS website). On the basis of the frequency and type of activity, a physical activity score was derived for each man, from which a six-level index was created (none, occasional, light, moderate, moderately vigorous, and vigorous). These exposure categories displayed strong relations with both pulse rate and FEV1.17

Follow-up questionnaires and screenings

At each of the follow-up questionnaires (Q5, Q92, Q96, and Q20), surviving study participants were asked about their smoking habits and (with the exception of Q5) about their level of physical activity. From these data, smoking status and physical activity were recategorized at each time point according to the baseline definitions so that each man may have had in addition to their baseline recorded level up to four follow-up measures of cigarette smoking exposure (taken at Q5, Q92, Q96, and Q20) and up to three follow-up measures of physical activity (taken at Q92, Q96, and Q20). After 20 years of follow-up, all surviving men were invited to attend for a rescreening at which BMI was measured. Using these data together with measured BMI from men in two towns who took part in a separate substudy in 199618 and from men in a North London general practice who took part in a 1 week repeatability study in 2000, information on variation in measured BMI over periods of 1 week and approximately 4, 16, and 20 years was ascertained.19 From these data, the regression dilution ratio for BMI over a 10 year interval was estimated.

Assessment of incident major CVD

Information on incident mortality was collected through the established "tagging" procedures provided by the National Health Service registers, which provide automatic notification of death and its cause. Fatal coronary events were defined as deaths from ischaemic heart disease, including sudden death of presumed cardiac origin (ICD-9 code of 410–414), and fatal strokes were defined as deaths with an ICD-9 code of 430–438. Non-fatal heart attacks and strokes were ascertained from general practitioner reports supplemented by systematic 2-yearly patient record reviews throughout the study period.20 Non-fatal heart attacks were diagnosed according to the established WHO criteria, whereas non-fatal strokes were defined as all cerebrovascular events, which produced a neurological deficit present for >24 h.21 In this paper, major CVD events include death from coronary heart disease or stroke and non-fatal myocardial infarction or stroke.

Average lifestyle risk factor levels during the study

Using the baseline data, together with data from (potentially) each of the four follow-up questionnaires, 'average' exposures to cigarette smoking and physical activity over the study period (or until the time to first major CVD event if observed) were calculated for each individual. For cigarette smoking, men were defined as being either never smokers or ex-smokers throughout the study if they were defined as such at each questionnaire they responded to. For men who were current smokers at baseline, the number of cigarettes they reported smoking at each questionnaire (zero if they had given up) was used to calculate the average number of cigarettes they smoked per day during the study. It was assumed that any changes in the number of cigarettes smoked between the consecutive questionnaires occurred linearly over the intervening period, unless a major CVD event occurred during that period in which case it was assumed that the individual continued to smoke at the same rate as reported at the most recent questionnaire until the date of that event (note that this is equivalent to assuming that changes in the risk factor occur at the mid-point of the interval between the two questionnaires). Men who were non-smokers at baseline (never- or ex-smokers) but subsequently reported to be current smokers were classified as 'new/recurrent' smokers. This approach of reclassifying smoking status from information provided by all the questionnaires should lead to exposure categories that 'best represent' each individual’s risk level. For physical activity, a six-point scale was used to denote the activity level at the baseline assessment and each of the follow-up assessments [from 0 (none) to 5 (vigorous)]. Using these data, 'average' physical activity level was calculated (changes between questionnaires were again assumed to occur linearly unless the individual had a major CVD event during that time). From these average exposure levels, each individual was reclassified on the original categorical scale, e.g. an average exposure of <0.5 was defined as 'none', and 0.5–1.49 was defined as 'occasional', etc. For BMI, the estimated usual level 10 years after baseline (the mid-point of the follow-up interval) was calculated from the baseline level and the estimated regression dilution ratio using regression calibration.
Statistical analyses

For men with no baseline evidence of CVD, Cox proportional hazards regression was used to estimate the age-adjusted relative hazard of major CVD and all-cause mortality over 20 years by fifth of the baseline distribution of BMI and by baseline cigarette smoking and physical activity group; proportional hazards were assessed through examination of the Schoenfeld residuals. Point estimates of hazard ratios are displayed in figures as floating absolute risks. This does not alter the values but ascribes an appropriate variance to each group (rather than having variances for each group relative to one group that is arbitrarily chosen to have a relative hazard of one and no associated error). The relative informativeness of baseline vs. average exposures to cigarette smoking and physical activity was evaluated through examination of the \( \chi^2 \) likelihood ratio statistics in the Cox proportional hazards model. A ‘low-risk’ group of men was subsequently defined as men who had never regularly smoked cigarettes, were at least moderately active during the study, and had a BMI of not >25 kg/m\(^2\). The risks of major CVD and all-cause mortality over 20 years for this ‘low-risk’ group were compared with those of men with one, two, and all three of the ‘high-risk’ factors by plotting Kaplan-Meier cumulative incidence curves; differences between these curves were assessed using the log-rank test. For each of the high-risk groups, the marginal population attributable risk fraction corresponding to the \( k \)th group (PARF\(_k\)) was estimated by the equation

\[
\text{PARF}_k = \frac{p_k (R_{R_k} - 1)}{1 + \sum p_k (R_{R_k} - 1)}
\]

where \( p_k \) is the proportion of the population in the \( k \)th group and \( R_{R_k} \) is the relative risk of the event (approximated by the relative hazard in a Cox model)\(^{24} \) when compared with the ‘low-risk’ group (the men with no high-risk factors). The overall combined PARF is equal to the sum of the marginal PARFs. The 95% confidence intervals for these estimates were estimated using a bias-corrected bootstrap resampling method.\(^{25} \)

Results

Study participants

Of the 7735 men recruited into the study, 1186 (15.3%) had baseline evidence of CVD (symptoms or diagnosis). Of the remaining men, 6452 (99%) had complete baseline information on cigarette smoking, physical activity, and BMI. The baseline characteristics of these men, together with the estimated usual (average) risk exposure levels during the study, are shown in Table 1. Average BMI was just over 25 kg/m\(^2\), and three-quarters of the men were either currently, or had ever been, regular cigarette smokers. Approximately two-thirds of the men either did not exercise, or did so only occasionally, or to a light level during their ‘exposure period’. Risk factor levels derived from the baseline measures tended to overestimate the proportion of men who were truly heavy smokers during the follow-up period, and to overestimate the proportion of men at the ‘extremes’ of the physical activity distribution. The effect of within-person variation (regression dilution bias) on BMI was minimal; the estimated regression dilution ratio for BMI (over a 10 year period) was 0.97, indicating virtually no within-person variation in this exposure over time.

Lifestyle characteristics, major CVD, and all-cause mortality

Of the 6452 men with complete information on lifestyle characteristics, 1194 (18.5%) had a major CVD event within 20 years and 1525 (23.6%) died of all causes. The age-adjusted relationships between lifestyle coronary risk factors (cigarette smoking, physical activity, and BMI) and the 20 year risk of major CVD and all-cause mortality are shown in Figures 1–3 and Tables 2 and 3, both before and after correction for within-person variation.

Cigarette smoking

Relative to individuals who had never smoked cigarettes, ex-smokers had a 22% higher risk of CVD according to the baseline data (Figure 1). This was little changed after adjustment for within-person variation, because of the observation that the group of men who were new/recurrent smokers (predominantly men who were ex-smokers at baseline but current smokers at some point subsequently) had a similar excess risk of major CVD over never smokers. When baseline data were used to define smoking exposure, CVD risk increased with the number of cigarettes smoked each day up to 21–39 cigarettes, but no further increases in risk were observed at higher smoking levels. However, when reported changes in cigarette smoking habits over time were taken into account, major CVD risk increased linearly with the number of cigarettes smoked each day. Similar findings were observed for all-cause mortality. Smoking exposure after adjustment for within-person variation was observed to be 51% more informative at predicting major CVD (likelihood ratio contributions, 157 vs. 104) and to be 24% more informative at predicting all-cause mortality.

Table 1 Baseline and ‘usual’ lifestyle characteristics of 6452 men in the BRHS with no baseline evidence of CVD and complete risk factor data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline level</th>
<th>Usual level(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (year)</td>
<td>49.2 ± 5.8</td>
<td>—</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>25.4 ± 3.2</td>
<td>25.4 ± 3.1</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked cigarettes</td>
<td>1601 (24.8)</td>
<td>1586 (24.6)</td>
</tr>
<tr>
<td>Ex-cigarette smoker</td>
<td>2248 (34.8)</td>
<td>2101 (32.6)</td>
</tr>
<tr>
<td>New/recurrent cigarette smoker</td>
<td>—</td>
<td>162 (2.5)</td>
</tr>
<tr>
<td>Current smoker (1–20 per day)</td>
<td>1641 (25.4)</td>
<td>2012 (31.2)</td>
</tr>
<tr>
<td>Current smoker (21–39 per day)</td>
<td>707 (11.0)</td>
<td>513 (8.0)</td>
</tr>
<tr>
<td>Current smoker (40 or more per day)</td>
<td>255 (4.0)</td>
<td>78 (1.2)</td>
</tr>
<tr>
<td>Physical activity level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>505 (7.8)</td>
<td>344 (5.3)</td>
</tr>
<tr>
<td>Occasional</td>
<td>1934 (30.0)</td>
<td>1758 (27.3)</td>
</tr>
<tr>
<td>Light</td>
<td>1490 (23.1)</td>
<td>1822 (28.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1053 (16.3)</td>
<td>1267 (19.6)</td>
</tr>
<tr>
<td>Moderately vigorous</td>
<td>1001 (15.5)</td>
<td>927 (14.4)</td>
</tr>
<tr>
<td>Vigorous</td>
<td>469 (7.3)</td>
<td>334 (5.2)</td>
</tr>
</tbody>
</table>

\(^{a}\)Estimated from the baseline level after taking any ‘within-person variation’ prior to a major CVD event into account.

\(^{b}\)Men who reported to be non-smokers at baseline but subsequently reported to be current smokers during follow-up.
Figure 1  Risk of major CVD and all-cause mortality by cigarette smoking exposure. The black circles correspond to baseline smoking groups and the white circles to true usual smoking groups obtained after taking within-person variation into account.

Figure 2  Risk of major CVD and all-cause mortality by physical activity level. The black circles correspond to baseline physical activity groups and the white circles to true usual physical activity level obtained after taking within-person variation into account.

Figure 3  Risk of major CVD and all-cause mortality by BMI. The black circles correspond to baseline levels and the white circles to usual levels during the study.
(likelihood ratio contributions, 281 vs. 227) than baseline cigarette smoking exposure. Examination of the Schoenfeld residuals for the relationship between cigarette smoking and major CVD revealed significant ‘non-proportionality’. Associations were stronger in the early years of follow-up than in the later years. This is consistent with previous studies which have demonstrated that the relative risk associated with current smoking decreases with increasing age.5

Physical activity
For physical activity (Figure 2), major CVD risk was highest among inactive men and decreased progressively with increasing levels of physical activity up to moderate levels, after which no further decreases in risk were observed. The relative risk reduction corresponding to vigorous levels of physical activity was similar before and after correction for within-person variation, the vigorously active had approximately half the risk of major CVD of the inactive. Again, a similar relationship was observed for all-cause mortality, when compared with inactive men, the risk of dying in any given year for moderately active men was 35% lower (before) and 62% lower (after) correction for within-person variation. The informativeness of the six-level physical activity score was also improved by taking within-person variation into account (the likelihood ratio statistics increased by 49%, from 197 to 294, for major CVD, and by 36%, from 335 to 457, for all-cause mortality).

Body mass index
Figure 3 shows the relationships between the BMI and the risk of major CVD and all-cause mortality. Major CVD risk decreased steadily with decreasing BMI, at least down to a level of 21 kg/m². The effects of within-person variation (regression dilution bias) for BMI were minimal, because of the stability of this measure over time. For each 1 kg/m² increase in BMI, the risk of major CVD was estimated to increase by 6% (96% CI 4–7%). For all-cause mortality, a U-shaped relationship was observed, with men with a BMI of approximately 23 kg/m² appearing to have the lowest 20 year risks.

Combined influence of lifestyle characteristics on major CVD and all-cause mortality
For assessing major CVD risk associated with multiple adverse lifestyle characteristics, individuals were separated into four categories (Table 4). A ‘low-risk’ group was defined as those who had never regularly smoked cigarettes, were at least moderately active, and had a BMI of no more than 25 kg/m² during the period of risk exposure (period ‘at risk’ of first major CVD event). After correction for within-person variation, 369 men (5.7%) were classified into this low-risk group, 1609 men (24.9%) were identified as having one of these high-risk factors, 2758 men (42.8%) as having two of these factors, and 1716 men (26.6%) as having all three high-risk factors (the size of these groups, and the men included in each of them, were virtually the same when derived from baseline data). Estimates of relative risks and marginal population attributable risk fractions for the three high-risk groups, both before and after correction for within-person variation, are shown in Table 4; the cumulative incidence of major CVD and all-cause mortality over 20 years for these four groups (none, one, and two and three risk factors; after correction for within-person variation) are shown in Figure 4.

After correction for within-person variation, men with one high-risk factor (ever a cigarette smoker, physically

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**Table 2** Risk of major CVD and all-cause mortality by cigarette smoking exposure

<table>
<thead>
<tr>
<th>Cigarette smoking</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline exposure</td>
<td>Usual exposure</td>
</tr>
<tr>
<td>Never smoked cigarettes</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ex-cigarette smoker</td>
<td>1.22 (1.03, 1.45)</td>
<td>1.21 (1.02, 1.44)</td>
</tr>
<tr>
<td>New/recurrent cigarette smoker</td>
<td>1.16 (0.75, 1.78)</td>
<td>1.16 (0.75, 1.78)</td>
</tr>
<tr>
<td>Current smoker (1–20 per day)</td>
<td>1.82 (1.53, 2.16)</td>
<td>1.62 (1.37, 1.92)</td>
</tr>
<tr>
<td>Current smoker (21–39 per day)</td>
<td>2.41 (1.97, 2.93)</td>
<td>3.30 (2.68, 4.04)</td>
</tr>
<tr>
<td>Current smoker (40 or more per day)</td>
<td>1.70 (1.24, 2.34)</td>
<td>4.10 (2.71, 6.22)</td>
</tr>
</tbody>
</table>

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**Table 3** Risk of major CVD and all-cause mortality by physical activity level

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline exposure</td>
<td>Usual exposure</td>
</tr>
<tr>
<td>None</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Occasional</td>
<td>0.76 (0.62, 0.93)</td>
<td>0.61 (0.49, 0.75)</td>
</tr>
<tr>
<td>Light</td>
<td>0.69 (0.56, 0.85)</td>
<td>0.43 (0.34, 0.53)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.54 (0.43, 0.69)</td>
<td>0.34 (0.27, 0.43)</td>
</tr>
<tr>
<td>Moderately vigorous</td>
<td>0.55 (0.43, 0.69)</td>
<td>0.39 (0.30, 0.50)</td>
</tr>
<tr>
<td>Vigorous</td>
<td>0.54 (0.41, 0.73)</td>
<td>0.47 (0.34, 0.64)</td>
</tr>
</tbody>
</table>
inactive, or overweight) had over twice the risk of major CVD when compared with men with one, two, or all three of these risk factors (groups defined after taking within-person variation into account).

Table 4 20 year relative risks and marginal population attributable risk fractions for major CVD and all-cause mortality corresponding to men with one, two, or three high risk factors present relative to men with no high-risk factors (the low-risk group)

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Number of men (%)</th>
<th>Major CVD</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR (95% CI)</td>
<td>PARF a (95% CI)</td>
</tr>
<tr>
<td>Before correction for within-person variation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No risk factors</td>
<td>382 (5.9)</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>One risk factor</td>
<td>1606 (24.9)</td>
<td>2.02 (1.33, 3.05)</td>
<td>9 (5, 13)</td>
</tr>
<tr>
<td>Two risk factors</td>
<td>2752 (42.7)</td>
<td>2.82 (1.89, 4.21)</td>
<td>29 (20, 34)</td>
</tr>
<tr>
<td>Three risk factors</td>
<td>1712 (26.5)</td>
<td>3.54 (2.36, 5.31)</td>
<td>25 (19, 29)</td>
</tr>
<tr>
<td>All high-risk men combined</td>
<td>6070 (94.1)</td>
<td>2.79 (1.88, 4.15)</td>
<td>63 (47, 76)</td>
</tr>
<tr>
<td>After correction for within-person variation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No risk factors</td>
<td>369 (5.7)</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>One risk factor</td>
<td>1609 (24.9)</td>
<td>2.12 (1.38, 3.26)</td>
<td>10 (5, 13)</td>
</tr>
<tr>
<td>Two risk factors</td>
<td>2758 (42.8)</td>
<td>3.02 (1.99, 4.58)</td>
<td>30 (22, 35)</td>
</tr>
<tr>
<td>Three risk factors</td>
<td>1716 (26.6)</td>
<td>3.82 (2.51, 5.81)</td>
<td>26 (21, 30)</td>
</tr>
<tr>
<td>All high-risk men combined</td>
<td>6083 (94.3)</td>
<td>2.98 (1.97, 4.51)</td>
<td>66 (47, 72)</td>
</tr>
</tbody>
</table>

*The marginal PARFs displayed are a function of both the relative risk and the proportion of men falling into that group. Therefore, even if the relative risk corresponding to a high-risk group is large, the PARF may be small if few men fall into that category. The overall combined PARF for all three high-risk groups combined is the direct sum of the marginal PARFs (Methods). PARF values are expressed as percentages.

Discussion

In middle-aged British men with no previous history of diagnosed CVD, major CVD and all-cause mortality rates in non-smoking, physically active, and non-overweight men were...
61–66% lower than for men with one or more of these risk factors. If all men had experienced the risks of this low-risk group, 66% of major CVD events and 60% of all deaths during this period would have been prevented or postponed. By correcting for within-person variation in lifestyle risk factors, exposure categories were defined that were more informative at predicting disease risk, and estimated risk associations were magnified, particularly for the risks associated with continued heavy smoking and the benefits of regular physical activity.

Validity and importance of correcting for within-person variation

The analyses presented in this paper show that three lifestyle characteristics, cigarette smoking, physical activity, and BMI, are strongly related to subsequent risks of major CVD and all-cause mortality. In making these assessments, our analyses have taken into account the influence that within-person variation in these factors over time may have on estimated disease relationships. For the categorical risk factors, an ‘averaging approach’ was used to define exposure categories (to take into account information supplied by the follow-up questionnaires), a method that has been used elsewhere. The key feature of this approach that greatly affects its validity in this setting is that only information on risk factor changes obtained, while individuals were still at risk of a first major CVD event was used to derive the summary average exposures. This is important to remove the effect that the occurrence of disease could have on lifestyle characteristics. Adjusting for within-person variation in this way led to summary measures that were more ‘informative’ at predicting major CVD and all-cause mortality than the baseline measures alone and revealed larger risk differences across different levels of cigarette smoking and physical activity than were apparent when using baseline data. Observational studies (and in particular those with long follow-up periods) should therefore make every attempt to take these influences into account. Unfortunately, it would appear that most studies currently rely solely on baseline measurements of risk factors. In contrast to our observations for cigarette smoking and physical activity, we found relatively little within-person variation in BMI (and hence little impact of adjustment for it). Similarly, when individuals were grouped into risk categories based on their cigarette smoking status, physical activity level, and BMI, correction for within-person variation had only a small effect on estimated risk differences and population attributable risk fractions (Table 4). This is because the low risk reference group included only men who were never smokers (a group virtually unchanged by adjustment for within-person variation in cigarette smoking), moderately active (a group that, because most of the variation in physical activity occurred at the opposite extremes of the distribution, was also fairly robust to misclassification error), and not overweight (a group that again was virtually unchanged by adjustment for within-person variation, because of the previously described ‘robustness’ of baseline BMI). The real value of correcting for within-person variation in our analyses was therefore in determining the true extent of differences in major CVD risk and all-cause mortality across the entire spectrum of the cigarette smoking and physical activity distributions. Although the results of this study are directly applicable only to British men, they may also be of considerable relevance to other populations, particularly to studies on women (though this will depend on the extent that relative risks and risk factor distributions are similar in both sexes).

Comparison with other studies

Our estimates of the risks of major CVD associated with cigarette smoking, physical inactivity, and increased BMI (before adjustment for within-person variation) are generally consistent with previous studies of coronary heart disease (CHD) and stroke. In a case–control study of 14 000 survivors of myocardial infarction (and 32 000 controls), cigarette smokers had about five times the risk of myocardial infarction of non-smokers at age 40–49, three times the risk at age 50–59, and 2.5 times the risk at age 60–69. In comparison, in the 40 year report from the British Doctors Study, the rate of vascular deaths (predominantly ischaemic heart disease and stroke) was 58% higher in cigarette smokers than never-smokers (1643 vs. 1037 deaths per 100 000 men per year). The 50 year report showed that when compared with non-smokers, men who smoked throughout the study had two to three times the risk of dying in middle age (35–69 years). For physical activity, a meta-analysis of its effects on CHD risk published in 1990 found that those in ‘active’ occupations had approximately half the risk of CHD than those in sedentary occupations. These data have recently been supported by a review of the effects of physical activity on the risk of all CVD, which concluded that being physically active was associated with about a 40–50% reduction in the risk of CVD. These are consistent with the estimate presented in this paper before within-person variation was taken into account (46% relative risk reduction for moderate levels of physical activity; Table 3). However, after taking within-person variation in physical activity into account, moderately active men were observed to have a 66% lower risk of major CVD than inactive men. However, this estimate of the potential true benefit of physical activity is difficult to assess in the context of other studies, because of the few studies that have attempted to control for within-person variation. However, one study that did use repeated measurements of physical activity exposure to quantify ‘physical activity group’ found that women who (on average) walked for at least 2 h a week had a 67% lower risk of CHD than women who did not walk regularly. Our estimates of the relationship between BMI and CVD risk are also in agreement with previous publications. In an overview of 33 cohorts from the Asia Pacific region, a 1 kg/m² increase in BMI was also associated with a 6% increase in risk of CHD, whereas in Finnish men aged 30–59, CHD risk increased by 4% for a 1 kg/m² increase in BMI. In Chinese adults, a recent meta-analyses reported that CVD risk increased by 7% and stroke risk by 3% for each 1 kg/m² increase in BMI. Our observation of a U-shaped relationship between BMI and all-cause mortality is also consistent with many previous studies. Our analyses of the combined contribution of these three lifestyle risk factors to CVD risk build on earlier work by taking account of within-person variation in these factors. In a previous analysis of the BRHS carried out after 15 years of follow-up, the predicted 15 year probability of
major CVD or diabetes in men aged 50 and initially free from CVD or diabetes ranged from 11% in non-smoking, moderately active men with a BMI of $\leq 24$ kg/m² to 58% in inactive, obese (BMI $\geq 30$ kg/m²) smokers, approximately a five-fold difference in risk. Extending these analyses to 20 years of follow-up, the relative hazard of major CVD for this very high-risk group, compared with this low-risk group, was 5.8 (95% CI 2.5–13.7) and the relative hazard of all-cause mortality was 5.9 (95% CI 2.9–12.1). These very large differences in risk, though based on relatively few individuals at opposite ends of the risk spectrum, highlight the crucial importance of lifestyle characteristics in determining individual levels of risk. Importantly, however, with the current increasing trends in obesity and sedentary behaviour, the proportion of the population falling into this high-risk group (and hence the contribution of this group to population levels of disease) is likely to increase substantially in the coming decades.

Role of other established cardiovascular risk factors

In this paper, we excluded the effects of blood cholesterol and blood pressure on CVD risk from our analyses, because the mechanisms by which lifestyle risk factors influence CVD risk are likely to be mediated, at least partially, through their effects on these factors (adjustment for them would result in underestimation of the true importance that lifestyle has on CVD risk). In a previous analysis, however, we showed that these two risk factors (when considered with cigarette smoking) can account for the majority of CVD cases that occur in a population (in direct contrast to the ‘only 50%’ myth) and that modest downward shifts in the population distributions of these factors could lead to unexpectedly large reductions in population levels of disease. Analysis of time trends in the UK provide supporting evidence, indicating that (even without further gains from medical treatments) continuation of current trends in cigarette smoking, blood pressure, and blood cholesterol alone could lead to around 24 000 fewer premature CHD deaths being observed in 2010 in the UK than were observed in 1994. We have also excluded alcohol consumption from the list of lifestyle factors considered. The relationship between alcohol and CVD (and total mortality) has consistently been shown to be U- (or J-) shaped, with individuals who drink light to moderate amounts of alcohol generally being around 25–30% less likely to experience CVD than individuals who do not drink. Although it is generally now accepted that this relationship is likely to be causal (because of haematological effects including beneficial effects on HDL cholesterol), we decided to exclude it from analyses because of the range of difficulties in recommending alcohol consumption for health reasons (such as the range of other health and social problems associated with alcohol, the risks associated with heavy drinking, and the observation that many non-drinkers abstain for a particular reason, for example, religion, previous health conditions, or a family history of alcoholism). Including regular heavy drinking as a fourth ‘high-risk’ category did not change the estimate of the combined population attributable risk fraction, as these men were already defined as ‘high-risk’ based on their levels of cigarette smoking, physical activity, and BMI.

Implications for the primary prevention of CVD

The findings from this paper have important implications for CVD prevention. They confirm the findings of many previous studies concerning the risks associated with cigarette smoking, physical inactivity, and increased BMI and suggest that (because of the effects of within-person variation) these risks may be even greater than previously estimated. Importantly, the estimated combined contribution of these factors to population levels of CVD (and premature all-cause mortality) suggests that factors associated with a healthy lifestyle should not be underestimated when considering the role they can have for the primary prevention of CVD. Although these estimates of the benefits of a healthy lifestyle correspond to long-term lifestyle characteristics, substantial benefits are also achievable through lifestyle modification in adulthood. There is a strong evidence showing that smoking cessation and taking up physical activity, even in the elderly, reduces the risk of subsequent CVD although the influence of weight reduction in adulthood on future CVD risk is less clear. In fact, the observation that BMI was relatively little affected by within-person variation may suggest that this factor is less amenable to change over time than cigarette smoking or physical activity, indicating that prevention policies may be better directed towards promoting and maintaining physical activity, rather than at reducing weight per se. However, it is the long-term benefits on CVD risk of population-wide changes in lifestyle modification that are note worthy; men with no adverse lifestyle characteristics had a 53% lower risk of major CVD than men with one risk factor, a 67% lower risk than men with two factors, and a 74% lower risk than men with all three risk factors (Table 4). These differences in risk are similar to, if not larger than, any risk reductions likely to be achievable through multiple drug interventions (for instance, we have previously estimated that a combination of a statin, aspirin, a β-blocker, and an ACE inhibitor could reduce major CVD risk in men by approximately 68%, though others have suggested that larger risk reductions of the order to 80–85% may be possible from alternative drug regimes). Although population-wide multiple drug treatment of asymptomatic individuals has recently received much attention (e.g. the ‘polypill’ approach), the disadvantages and costs involved with ‘medicalising’ the entire ‘healthy’ population should not be forgotten. In addition, such an approach would do nothing to tackle the underlying causes that make CVD common, or to reduce the supply of middle-aged people requiring drug treatment. Most, if not all, of the benefits from these approaches (without any of the risks) could equally be achieved through long-term population-wide improvements in lifestyle characteristics.

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