

Impact of lifestyle in middle-aged women on mortality: evidence from the Royal College of General Practitioners' Oral Contraception Study

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ABSTRACT

Background

Although many individuals have multiple lifestyle risk factors, few studies have investigated the impact of lifestyle risk factor combinations among women.

Aim

To investigate the relationship between individual and combinations of lifestyle risk factors in middle-aged women with subsequent mortality, and to estimate the associated population attributable risks.

Design of study

Prospective cohort study.

Setting

Royal College of General Practitioners' (RCGP) Oral Contraception Study, UK.

Method

In 1994–1995, women remaining under follow-up in the RCGP Oral Contraception Study were sent a lifestyle survey, from which modifiable risk factors were identified: pack-years smoked, physical inactivity, never drinking versus consuming at least 7 units of alcohol weekly, and being underweight, overweight, or obese. The cohort was followed to December 2006 or death. Population attributable risks were calculated.

Results

Of 10 059 women studied, 896 died. Pack-years smoked (11–20 years: adjusted hazard ratio [HR] = 1.82, 95% confidence interval [CI] = 1.46 to 2.27; >20 years: adjusted HR = 2.34, 95% CI = 2.00 to 2.74); never drinking alcohol (adjusted HR = 1.66, 95% CI = 1.34 to 2.05); being underweight (adjusted HR = 1.66, 95% CI = 1.03 to 2.68); and physical inactivity (<15 hours/week: adjusted HR = 1.73, 95% CI = 1.46 to 2.04) were significantly associated with mortality compared with their respective reference group. Women with multiple lifestyle risk factors had higher mortality risks than those reporting one factor. The population attributable risk of the combination of smoking, physical inactivity, body mass index outside normal range, and alcohol (never drinking or excess intake) was 59% (95% CI = 31% to 78%).

Conclusion

Assuming a causal relationship between lifestyle and mortality, avoidance of four lifestyle risk factors would have prevented 60% of the deaths. The importance of avoiding smoking and undertaking physical inactivity during midlife should continue to be emphasised.

Keywords

epidemiology; follow-up studies; lifestyle; mortality; women.

INTRODUCTION

Worldwide, including in the UK, cardiovascular disease and cancer remain leading causes of morbidity and death among postmenopausal women.^{1–3} The relationships between modifiable lifestyle risk factors and cardiovascular disease⁴ and cancer⁵ are well established. Many individuals will have more than one lifestyle risk factor, yet few studies have investigated the impact of combinations of risk factors, particularly among middle-aged women.^{6,7}

The Nurses' Health Study evaluated the impact of lifestyle factor combinations on mortality in 77 782 women in the US, aged 34–59 years, who were followed for 24 years.⁶ Compared with women who had none of the lifestyle risk factors, those with five risk factors (smoking, overweight, low physical activity, poor diet, and heavy drinking or alcohol abstinence) had a more than fourfold statistically significant increased mortality risk. An estimated 58% of the deaths were attributed to these lifestyle risk factors.

The European Prospective Investigation of Cancer (EPIC)-Norfolk study examined the impact of

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How this fits in

The relationship between modifiable lifestyle risk factors, serious morbidity, and death is well established, yet few studies have investigated the impact of combinations of risk factors, particularly among women. This study investigated the relationship between modifiable lifestyle risk factors and all-cause mortality in women recruited in the UK for the Royal College of General Practitioners' Oral Contraception Study, and the proportion of deaths in the cohort that could have been avoided if the women had followed a healthy lifestyle was calculated. Assuming a causal relationship between lifestyle and mortality, nearly 60% of the deaths could have been prevented by avoidance of four modifiable risk factors: smoking, physical inactivity, body mass index outside normal range, and excess alcohol intake or never drinking. Smoking and physical inactivity had the highest population attributable risks when examined alone or in combination with other risk factors, emphasising the importance of avoiding smoking and undertaking physical activity during midlife.

combinations of lifestyle factors on mortality during an 11-year follow up of 9181 males and 11 063 females in the UK aged 45–79 years at recruitment.⁷ In females, the combination of smoking, physical inactivity, not having a moderate alcohol intake, and low fruit and vegetables intake was associated with a fivefold higher mortality risk than among women with none of these risk factors. Population attributable risks were not calculated, so the potential population impact of avoiding this combination of lifestyle risk factors among these UK women remains unknown. The present study investigated the relationship between modifiable lifestyle risk factors and all-cause mortality in women recruited for the UK's Royal College of General Practitioners' (RCGP) Oral Contraception Study.⁸ It also calculated the proportion of deaths that could have been avoided if the women had followed a healthy lifestyle.

METHOD

The RCGP Oral Contraception Study

The primary aim of the RCGP Oral Contraception Study is to investigate the long-term health effects of oral contraception. In 1968, 1400 GPs recruited 23 000 women who were using oral contraceptives and a similar number who had never done so.⁸ At recruitment, mean age of the women was 29 years (standard deviation [SD] = 6.6 years); all were married or living as married, and most (96%) were white European. Recruitment information included social class,⁹ number of cigarettes smoked daily, parity, details of previous use of oral contraceptives, and significant medical history. At 6-monthly intervals thereafter, the GPs provided details of any: hormonal preparations prescribed, pregnancies, surgery, new episodes of illness, and deaths.

During the mid-1970s, 75% of the cohort was 'flagged' at the NHS Central Registries for notification of future death and cancer registrations. The other women could not be flagged because they, or their GP, had already left the study. GP observation ceased in 1996 but notification of death and cancer registrations continues.

Health survey

Between November 1994 and July 1995, the GPs of the 12 303 women (26.5% of the original cohort) remaining under observation were asked to forward a health survey on the researchers' behalf.¹⁰ Most agreed, and 11 797 questionnaires were sent. To confirm that the GPs had distributed the questionnaires to the correct women, responders' reports of their date of birth, pregnancies, and history of hysterectomy were compared with information held in the Oral Contraception Study database.

As well as enquiring about current health status, the survey asked about modifiable lifestyle risk factors. Women were asked whether they had ever been a regular smoker of at least one cigarette daily for at least 1 year. If they had been such a smoker, they were asked about: age at starting and (if relevant) stopping smoking; number of cigarettes smoked previously and (if appropriate) currently; and number of years smoked. Pack-years smoked were then calculated.

Women were asked how often, on average, they drank alcohol (daily; 1–2 times per week; 1–2 times per month; 1–2 times per year, or never). 'Never drinkers' were asked if they had drunk alcohol previously. Alcohol drinkers were asked how many units they consumed in a typical week. To allow calculation of body mass index (BMI), women were asked for their height and weight.

Physical activity was assessed using two items from the short EPIC Physical Activity Questionnaire.¹¹ Participants were asked how many hours they spent, in a typical week in the previous year: gardening, walking (including walking to work, shopping, and leisure), cycling, and participating in other physical exercise (such as keep fit, aerobics, swimming, jogging, and tennis). For all activities, women were asked to report summer and winter hours separately. The second item asked if any of the activities had been practised vigorously enough to cause sweating or a faster heartbeat. If a participant indicated yes, they were asked to report the number of hours per week they practised vigorous activity. Similar to the EPIC-Norfolk study,⁷ summer and winter totals of each activity (regardless of whether vigorous) were averaged. A weekly total number of hours of activity was calculated and categorised into tertiles.¹² It was felt that the inclusion of housework in the weekly

physical activity total would have given a false impression of the cohort's activity levels. Additionally, the 2003 Health Survey for England found that domestic physical activity was common but not cardioprotective.¹³ Housework was therefore excluded from the physical activity estimates.

For health survey responders, information was extracted from the main Oral Contraception Study database about history of any serious illness (ischaemic heart disease, hypertension, stroke, venous thromboembolism, malignancy, diabetes mellitus, asthma, or bronchitis) by October 1994. Information was extracted about the date and cause

of death for women who subsequently died by 31 December 2006.

Statistical analysis

Data were analysed using SPSS (version 17.0) and SAS (version 9.1). Continuous variables were transformed into categorical variables.

Social class as assessed by husband's occupation was categorised as non-manual (classes I–IIIa and husbands recorded as students or commissioned armed forces), manual (classes IIIb–V and husbands recorded as non-commissioned armed forces), or missing.

Table 1. Lifestyle and sociodemographic characteristics associated with mortality among 10 059 responders to the health survey of the Oral Contraception Study.

Characteristic	<i>n</i>	%	<i>n</i> , died:alive	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio ^a (95% CI)
Age group, years					
<50	1750	17.4	46:1704	1.00	1.00
50–54	2724	27.1	141:2583	1.99 (1.43 to 2.78)	2.02 (1.45 to 2.82)
55–59	2572	25.6	199:2373	3.03 (2.20 to 4.17)	3.11 (2.25 to 4.29)
60–64	1855	18.4	228:1627	4.92 (3.58 to 6.75)	4.65 (3.38 to 6.41)
≥65	1158	11.5	282:876	10.45 (7.65 to 14.28)	9.18 (6.68 to 12.61)
Social class at recruitment					
Non-manual	3243	32.2	276:2967	1.00	1.00
Manual	6793	67.5	617:6176	1.07 (0.93 to 1.24)	1.06 (0.91 to 1.22)
Missing	23	0.2	3:20	1.56 (0.50 to 4.85)	2.00 (0.64 to 6.26)
Parity					
0	437	4.3	53:384	1.00	1.00
1–3	5418	53.9	415:5003	0.61 (0.46 to 0.81)	0.77 (0.58 to 1.03)
≥4	4202	41.8	428:3774	0.83 (0.62 to 1.10)	0.85 (0.64 to 1.14)
Missing	2	0.0	0:2	–	–
History of serious illness					
No	4862	48.3	268:4594	1.00	1.00
Yes	5197	51.7	628:4569	2.27 (1.97 to 2.62)	1.69 (1.46 to 1.96)
Number of pack-years smoked					
Never smoked	5204	51.7	327:4877	1.00	1.00
≤10	1096	10.9	74:1022	1.08 (0.84 to 1.39)	1.26 (0.98 to 1.62)
11–20	1020	10.1	105:915	1.67 (1.34 to 2.08)	1.82 (1.46 to 2.27)
>20	2180	21.7	326:1854	2.51 (2.15 to 2.93)	2.34 (2.00 to 2.74)
Missing	559	5.6	64:495	1.88 (1.44 to 2.46)	1.42 (1.08 to 1.86)
Number of units of alcohol/week					
Never drinks	806	8.0	112:694	2.09 (1.69 to 2.58)	1.66 (1.34 to 2.05)
<7	5504	54.7	381:5123	1.00	1.00
7–14	1381	13.7	107:1274	1.12 (0.91 to 1.39)	1.10 (0.89 to 1.37)
>14	388	3.9	40:348	1.52 (1.10 to 2.11)	1.34 (0.97 to 1.87)
Missing	1980	19.7	256:1724	1.94 (1.65 to 2.27)	1.49 (1.26 to 1.75)
Body mass index, kg/m ²					
<18.50 (underweight)	92	0.9	18:74	2.62 (1.63 to 4.19)	1.66 (1.03 to 2.68)
18.50–24.99 (normal)	4919	48.9	407:4512	1.00	1.00
25.00–29.99 (overweight)	3423	34.0	306:3117	1.08 (0.93 to 1.26)	0.98 (0.84 to 1.14)
≥30.00 (obese)	1468	14.6	146:1322	1.21 (1.00 to 1.46)	1.03 (0.85 to 1.24)
Missing	157	1.6	19:138	1.52 (0.96 to 2.41)	1.05 (0.66 to 1.66)
Hours of physical activity/week					
>28 (heavy)	3231	32.1	226:3005	1.00	1.00
15–28 (moderate)	3610	35.9	271:3339	1.08 (0.90 to 1.29)	1.14 (0.96 to 1.36)
<15 (light)	3058	30.4	368:2690	1.79 (1.52 to 2.11)	1.73 (1.46 to 2.04)
Missing	160	1.6	31:129	2.98 (2.05 to 4.34)	1.73 (1.18 to 2.55)

^aAdjusted for age, social class, parity, history of serious illness, pack-years of smoking, weekly alcohol intake, body mass index, and hours of physical activity/week. All variables were assessed at health survey except for social class which was recorded at recruitment to the Oral Contraception Study.

BMI was categorised as <18.50 kg/m² (underweight), 18.50–24.99 kg/m² (normal), 25.00–29.99 kg/m² (overweight), ≥30.00 kg/m² (obese), or missing.

Low risk was defined as never smoked, <7 units of alcohol weekly (but excluding never drinking), normal BMI, and physical activity >28 hours per week.

The relationship between lifestyle at the time at health survey completion and subsequent mortality was examined using Cox regression. Adjustments were made for potential confounding by age, social class, parity, and history of serious illness. Among women who answered all lifestyle items, the mortality effects of different combinations of modifiable lifestyle risk factors were examined. The reference group was women at low risk in all aspects of lifestyle. To facilitate this analysis, a binary variable was created for each lifestyle factor; that is, the low risk versus each of the different variable values.

To determine the population impact of lifestyle on mortality in the cohort, population attributable risks were calculated using an SAS macro.¹⁴ Population attributable risks estimate the proportion of deaths occurring in the population due to the exposure being investigated, assuming a causal relationship between exposure (lifestyle) and outcome (mortality).

RESULTS

The response rate to the health survey was 85.4% ($n = 10\,073$). Fourteen women whose survey information was not corroborated by the Oral Contraception Study dataset were excluded. Mean age of the responders was 56.1 years (SD =

6.5 years). Over two-thirds were of manual social class, less than 5% were nulliparous, and just over half had a history of serious illness (Table 1). Over 20% had smoked for more than 20 pack-years. Less than 4% reported drinking more than 14 units of alcohol weekly, and 8% were 'never drinkers', although one-fifth of responders had missing information about alcohol. One-third of 'never drinkers' had previously drunk alcohol. Although over half of responders had a BMI outside normal range, less than 1% were underweight. The threshold between the lowest and middle tertile of physical activity was 15 hours per week.

By December 2006, 896 (8.9%) responders had died, mainly from cancer ($n = 389$) or cardiovascular disease ($n = 267$). Median duration of follow-up was 141.7 months (interquartile range = 137.6 to 142.4 months). Following adjustment for potential confounding, compared with 'never smokers', those with ≥11 pack-years of smoking had a statistically significant increased mortality risk, with the largest risk in women who had smoked more than 20 pack-years (adjusted hazard ratio [HR] = 2.34, 95% confidence interval [CI] = 2.00 to 2.74, Table 1).

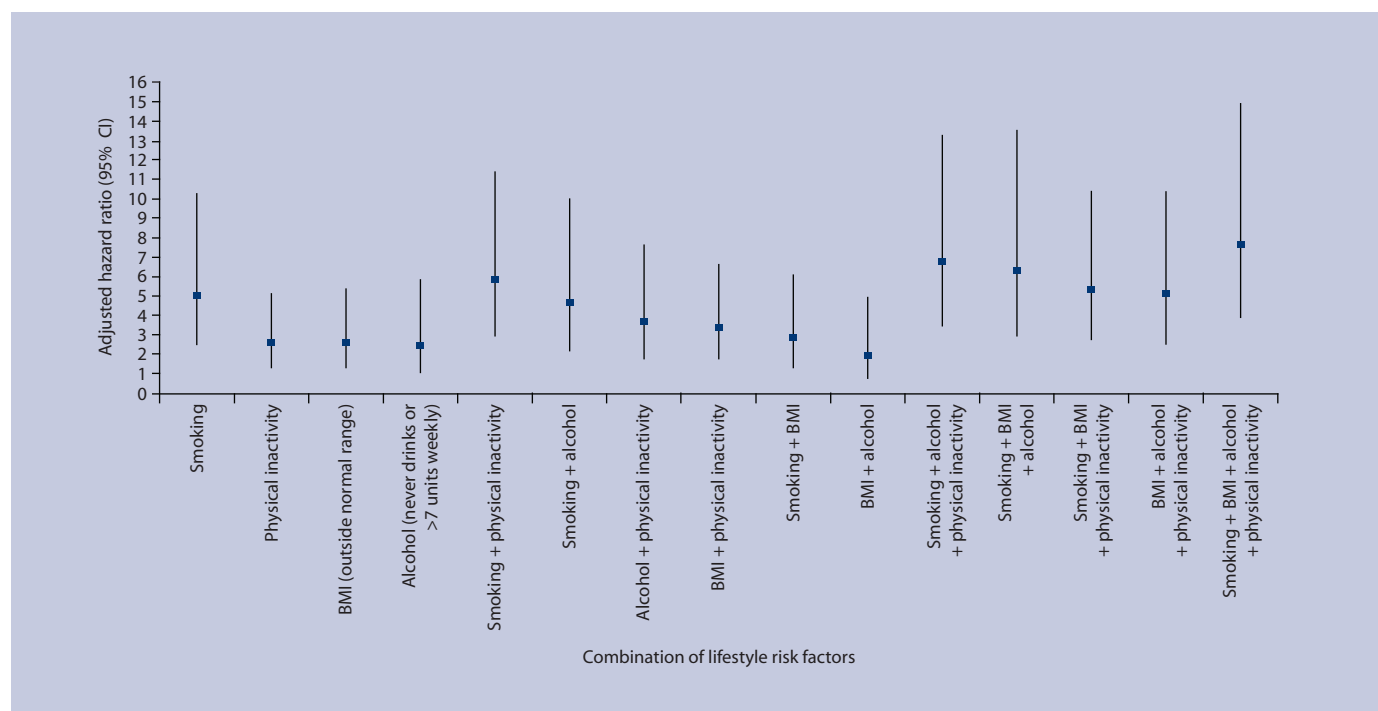
In comparison to women whose weekly alcohol consumption was less than 7 units, 'never drinkers' were more likely to die (adjusted HR = 1.66, 95% CI = 1.34 to 2.05). The increased mortality risk associated with more than 14 units of alcohol did not remain statistically significant after adjustment.

Although compared to women with a normal BMI, underweight women were nearly twice as likely to die (adjusted HR = 1.66, 95% CI = 1.03 to 2.68); obese

Table 2. Proportion of women with different combinations (and proportion with combination who died) of modifiable lifestyle risk factors.^a

Number of risk factors	Combination of risk factors	Women with combination, n (%)	% of women with combination who died
0	No risk factors	493 (6.5)	2.0
1	Smoking	347 (4.6)	9.5
	Physical inactivity	1004 (13.2)	4.8
	BMI	505 (6.6)	5.3
	Alcohol	217 (2.8)	5.1
2	Smoking + physical inactivity	693 (9.1)	10.4
	Smoking + alcohol	224 (2.9)	8.9
	Alcohol + physical inactivity	366 (4.8)	7.4
	BMI + physical inactivity	1054 (13.9)	6.5
	Smoking + BMI	331 (4.4)	6.0
	BMI + alcohol	177 (2.3)	4.5
3	Smoking + alcohol + physical inactivity	503 (6.6)	11.3
	Smoking + BMI + alcohol	169 (2.2)	11.8
	Smoking + BMI + physical inactivity	749 (9.9)	10.4
	BMI + alcohol + physical inactivity	333 (4.4)	10.2
4	Smoking + BMI + alcohol + physical inactivity	438 (5.8)	14.4

^aData from 2456 women with incomplete risk factor information excluded. Smoking = any pack-years of smoking. Physical inactivity = 28 hours or less per week. BMI = underweight, overweight, or obese body mass index. Alcohol = never drinks or >7 units per week.



women were not at significantly higher risk of death. Women in the most physically inactive group had a significantly higher mortality risk (adjusted HR = 1.73, 95% CI = 1.46 to 2.04) than those who were most active.

Three-quarters of responders ($n = 7603$, 75.6%) completed all of the lifestyle questions. Most of these women reported more than one lifestyle risk factor (5037/7603: 66.2%), although few (5.8%) had all four (Table 2). Among women who reported one risk factor, being physically inactive was the most common, followed by having a BMI outside normal range. More than 13% of the women reported the most frequent risk factor combination: a BMI outside normal range and being physically inactive. Less than 3% had the least frequent combination of: any pack-years of smoking, never drank alcohol or drank ≥ 7 units weekly, and were underweight, overweight, or obese. At the end of follow-up, 2.0% of the women with none of the risk factors, and 14.4% of those with all four risk factors, had died.

Most risk factor combinations were associated with a statistically significant increased mortality risk when compared with women without any of the risk factors (Figure 1). Among women with one lifestyle risk factor, the highest mortality estimates were associated with smoking. Although the confidence intervals for the risk estimates were wide and overlapping, the general pattern suggested that women with multiple risk factors had a higher mortality risk than those with one risk factor.

Smoking and physical inactivity had the highest population attributable risks when examined alone or

in combination with other risk factors (Table 3). If smoking, physical inactivity, BMI outside normal range, and excess alcohol consumption or never drinking had all been removed from the cohort, 59% (95% CI = 31% to 78%) of the deaths could have been avoided. The four lifestyle risk factors, together with age, social class, parity, and a history of serious illness gave a population attributable risk of 91% (95% CI = 59% to 98%).

Figure 1. Risk of mortality associated with different combination of lifestyle risk factors. Hazard ratios adjusted for age, social class, parity, and history of serious illness. BMI (outside range of normal body mass index).

Table 3. Population attributable risks (PAR) (95% CIs) of lifestyle risk factors associated with mortality during follow-up.

Risk factor(s)	PAR% (95% CI)
Smoking	33 (23 to 43)
Physical inactivity	25 (11 to 37)
BMI	2 (-11 to 15)
Alcohol	19 (8 to 30)
Smoking + physical inactivity	49 (31 to 64)
Smoking + BMI	35 (15 to 52)
Smoking + alcohol	46 (29 to 60)
Physical inactivity + BMI	26 (4 to 46)
Physical inactivity + alcohol	38 (18 to 56)
Alcohol + BMI	20 (-2 to 41)
Smoking + physical inactivity + BMI	50 (25 to 69)
Smoking + physical inactivity + alcohol	59 (36 to 74)
Smoking + BMI + alcohol	47 (22 to 66)
Physical inactivity + BMI + alcohol	39 (11 to 62)
Smoking + physical inactivity + BMI + alcohol	59 (31 to 78)

Smoking = any pack-years of smoking. Physical inactivity = 28 hours or less per week. BMI = underweight, overweight, or obese body mass index. Alcohol = never drinks or >7 units per week.

DISCUSSION

Summary of main findings

In this subset of women recruited to the Oral Contraception Study who completed a midlife health survey, ≥ 11 pack-years of smoking, never drinking alcohol, underweight BMI, and physical inactivity were each associated with an increased mortality risk more than a decade later. Generally, women who reported different combinations of lifestyle risk factors had a higher risk of death than those with only one factor. Assuming a causal relationship between lifestyle and mortality, in this cohort 59% of the deaths could have been avoided if all of the women were 'never smokers', physically active, and of normal BMI, and drank < 7 units of alcohol per week (while avoiding never drinking).

Strengths and limitations of the study

As all women were flagged at the NHS Central Registries, a study strength is the complete ascertainment of deaths. The prospective study design enabled estimation of both strength of association for different individual and combinations of lifestyle risk factors and subsequent death, and their public health importance in terms of population attributable risk. Population attributable risk assesses the magnitude of association and the risk factor prevalence in the population studied. Thus, lifestyle risk factors with modest effects can have a large population impact if they are common within the population; for example, physical inactivity in the present study. Conversely, strong associations for relatively rare risk factors produce more modest population attributable risks.

One limitation was the ability to include only women remaining under GP observation in 1994/1995 who completed the health survey. If women lost to follow-up differed systematically in their lifestyles from those who remained under follow-up, bias could have occurred. Women lost to follow-up before the cohort was flagged had similar recruitment characteristics to women under GP observation when flagging occurred.¹⁵ Furthermore, mortality rates were similar in women under GP observation and those flagged but no longer under GP follow-up, suggesting that loss to follow-up is unlikely to have substantially biased the findings.

The study results may have been affected by residual confounding, including confounding from lifestyle factors not measured such as diet. Lifestyle information was self-reported and assessed once. If there were systematic differences between different groups of women in accuracy of lifestyle reporting or in exposure changes over time, the study results will have been affected. Comparison of smoking

information at recruitment to the Oral Contraception Study with the health survey found that recruitment information underestimated smoking effects, as more women stopped smoking than started after recruitment.¹⁰ It can be assumed that changes in smoking habits among the cohort post-health survey have followed a similar pattern. It is difficult to estimate if, and in what direction, the other lifestyle risk factors have changed over time.

One-quarter of responders did not provide complete risk factor information; therefore, the number of women in some of the combinations of lifestyle factors was small, with imprecise risk estimates. Relatively few women died, so it was not possible to examine cause-specific mortality risks.

Comparison with existing literature

The study results concur with previous descriptions of a J- or U-shaped relationship between alcohol intake and mortality in women.^{16,17} It was not possible to determine how many of the women who reported never drinking were lifetime abstainers or who were former drinkers who had stopped for health reasons. As fewer than 4% of the cohort reported a weekly alcohol intake exceeding 14 units, the study possibly lacked statistical power (a type II error or beta effect) to detect any significant increased mortality risk associated with excessive drinking.

Similar to the present results, other UK prospective studies have found that physical inactivity⁷ and smoking^{7,18} in middle-aged women were associated with a significant increased mortality risk. In Scotland, the Renfrew and Paisley study found that in women the population attributable risk for all-cause mortality from smoking was 24.4% (95% CI = 20.3 to 28.5).¹⁹ The prevalence of smoking in the Renfrew and Paisley study differed from the present study and might account for the different population attributable risk estimates.

During a 40-year follow-up, being underweight or obese was associated with all-cause mortality among 644 women aged 35–70 years and living in London when recruited to the General Post Office study.¹⁸ The present study found evidence of a similar U-shaped relationship, although the increased risk in the obese group did not persist following adjustment for confounding.

Results are consistent with findings from the US.⁶ The Nurses' Health Study found the highest population attributable risk for smoking, followed by physical inactivity.⁶ None of the US cohort was underweight. Being overweight or obese had a higher population attributable risk (14.2%, 95% CI = 11.6 to 16.9) in the US cohort than that

associated with underweight, overweight, or obese BMI in the present study. Although the prevalence of being overweight or obese was identical (48%) in both studies, the absence of significant increased mortality risk associated with overweight or obesity at midlife in the present study accounts for the different population attributable risk estimates.

The population attributable risk for all-cause mortality associated with the combination of smoking, being overweight, having a poor diet, physical inactivity, and heavy alcohol consumption or abstinence was 58.1% (95% CI = 49.3 to 65.7%) in the US study. Although the present study did not examine the effect of diet, the US results were similar to the population attributable risk of 59% (95% CI = 31% to 78%) for all four lifestyle risk factors combined.

Implications for future research and clinical practice

Assuming a causal relationship between lifestyle and mortality, the study found that nearly 60% of deaths in this UK study of mostly white European middle-aged women could have been prevented by avoidance of four modifiable risk factors: smoking, physical inactivity, BMI outside normal range, and excess alcohol intake or never drinking. Smoking and physical inactivity had the highest population attributable risks when examined alone or in combination with other risk factors. The effect of different combinations of lifestyle risk factors on all-cause and cause-specific mortality risk among UK populations with different social and ethnic mix requires investigation. This study re-emphasises the importance of avoiding smoking and undertaking physical activity during midlife.

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Ethics committee

Although the Oral Contraception Study was established before the introduction of multicentre research ethics committees, the study was conducted in a manner consistent with the Declaration of Helsinki. Subject confidentiality was of paramount importance. Thus, all correspondence between participating GPs and the study coordinating unit used a unique study number, the key to which only the GPs knew. Data from the NHS central registries also use this unique study number, thereby avoiding the need for the study to hold identifying information.

Competing interests

The Centre of Academic Primary Care has received payments from Schering Plough and Wyeth Pharmaceuticals

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