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Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study

Sarah Wild*, Tracey Pierpoint*, Paul McKeigue* and Howard Jacobs†

**Epidemiology Unit, London School of Hygiene & Tropical Medicine and* †*Cobbold Laboratories, Department of Medicine, University College London Medical School, The Middlesex Hospital, London, UK*

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Summary

OBJECTIVE Polycystic ovary syndrome (PCOS) is associated with higher prevalence of cardiovascular risk factors but the relative prevalence of cardiovascular disease in women with PCOS has not previously been reported. We have compared cardiovascular mortality and morbidity in middle-aged women previously diagnosed with PCOS and age-matched control women.

DESIGN A retrospective cohort study of women diagnosed with PCOS in the United Kingdom before 1979.

PATIENTS Seventy cohort members died before 31 March 1999. Morbidity data were collected from 319 women with PCOS and 1060 age-matched control women. Sixty-one women with PCOS and 63 control women attended a clinical examination.

MEASUREMENTS Data were collected from death certificates, general practitioners' records and questionnaires with measurement of cardiovascular risk factors in a subsample of questionnaire respondents.

RESULTS All-cause and cardiovascular mortality in the cohort were similar to women in the general population (standardized mortality ratios (95% CI): 93 (72–117) and 78 (45–124), respectively). Women with PCOS had higher levels of several cardiovascular risk factors: diabetes ($P = 0{\cdot}002$) hypertension ($P = 0{\cdot}04$), hypercholesterolaemia ($P < 0{\cdot}001$), hypertriglyceridaemia ($P = 0{\cdot}02$) and increased waist:hip ratio ($P = 0{\cdot}004$). After adjustment for BMI, odds ratios (OR) were 2·2 (0·9–5·2) for diabetes, 1·4 (0·9–2·0) for hypertension and 3·2 (1·7–6·0) for hypercholesterolaemia. A history of coronary heart disease (CHD) was not significantly more common in women with PCOS (crude OR (95%CI) 1·5 (0·7–2·9)) but the crude OR for cerebrovascular disease was 2·8 (1·1–7·1).

CONCLUSION At long-term follow-up, a history of nonfatal cerebrovascular disease and cardiovascular risk factors including diabetes are more prevalent among women with polycystic ovary syndrome. Morbidity and mortality from of coronary heart disease among women with polycystic ovary syndrome is not as high as previously predicted. This finding challenges our understanding of the aetiology of coronary heart disease in women.

Polycystic ovary syndrome (PCOS), defined as a combination of oligomenorrhoea, infertility, acne and hirsutism with polycystic ovaries (Stein & Leventhal, 1935; Balen *et al*., 1995) is present in 5–10% of premenopausal women (Clayton *et al*., 1992; Polson *et al*., 1988). PCOS is associated with insulin resistance, upper body obesity and an unfavourable lipid profile (Burghen *et al*., 1980; Wild *et al*., 1985; Conway *et al*., 1992). It has been predicted that women with PCOS will be at increased risk of diabetes and coronary heart disease (CHD) (Dunaif, 1995) (Dahlgren *et al*., 1992a) but we have not previously been able to demonstrate a significant increase in cardiovascular mortality in a cohort of women with PCOS (Pierpoint *et al*., 1998).

Differences in risk factors between women with PCOS and controls may diminish with increasing age and could account for failure to detect excess risk of cardiovascular mortality among women with PCOS (James & Givens, 1979; Dahlgren *et al*., 1992b) (Legro *et al*., 1995; Talbott *et al*., 1998). To investigate this issue we undertook a follow-up study of the prevalence of cardiovascular risk factors and morbidity in surviving members of the cohort and have also analysed current mortality data.

Methods

The assembly of the cohort has been described in detail

Correspondence: Dr Sarah Wild, Health Care Research Unit, Mailpoint 805, Level B, South Academic Block, Southampton General Hospital, Southampton SO16 6YD, UK. Fax: +44 (0)2380 796529; E-mail: sarahwild@doctors.org.uk

previously (Pierpoint *et al*., 1998). Briefly, 1028 women diagnosed with PCOS before 1979 in the UK were identified from histopathology records (54%), operating theatre records of women who had undergone culdoscopy, wedge resection or biopsy of the ovary (22%), admission and discharge records (16%) and diagnostic indexes. Identifying details were forwarded to the National Health Service central registry (NHSCR) which provided death certificates and a list of Health Authorities/Boards with which surviving women in the UK were registered with a general practictioner (GP). National mortality rates were used to calculate the expected number of deaths from the number of woman-years at risk in each 5 year age group and 5 year calendar period. Standardized mortality ratios (SMR) were calculated as percentages of the ratio of observed to expected deaths.

Sample size

Based on estimated prevalences of CHD of 4% and of diabetes of 3% in the control group, a study of 240 women with PCOS and 720 controls has 90% power to detect risk ratios of 2·6 for CHD and 2·9 for diabetes in women with PCOS at 5% significance.

Follow-up

Approval for follow-up of the cohort was obtained from institutional and local ethical committees. Through Health Authorities we contacted the GPs of all traced survivors of the cohort below 75 years of age. We requested permission to review medical records of surviving cohort members with missing baseline clinical information and three age-matched control women. A questionnaire was sent to each cohort member under the age of 75 years that GPs gave permission to contact and to three age-matched control women for each cohort member. Control women were identified by being adjacent to the cohort member on the age–sex register at the same general practice after excluding relatives of the cohort member. Almost 100% of the population of middle-aged women in the United Kingdom is registered with a GP regardless of health status. This method of identifying controls provides a random population sample of women matched to cohort members for age and neighbourhood.

Clinical examination

Invitations to a clinical examination were sent to cohort members and to a single age-matched control for each cohort member who had responded to the questionnaire, were not known to have diabetes and who lived within one hour's journey from one of 11 study centres. Research nurses from the MRC practice framework were instructed in the protocol at a training day. Participants gave informed consent and two measurements each of waist and hip circumference were taken at the smallest girth between the costal margin and iliac crests and at the greater trochanters, respectively. Sitting blood pressures were measured twice in the right arm after participants had been resting for 5 minutes. Mean values for each individual were used in the analyses. Fasting blood samples were collected for measurement of glucose and lipids and a further sample was collected for measurement of glucose 2 h after a drink of Lucozade containing 75 g of glucose (SmithKline Beecham, London, UK).

Biochemical analyses

Blood samples were posted to the University Department of Clinical Biochemistry in Cambridge. Glucose was measured by the hexokinase-glucose-6-phosphate dehydrogenase method (Dade Dimension system, Dade International Inc., Newark, DE, USA). Cholesterol was measured using cholesterol esterase and oxidation of free cholesterol to produce hydrogen peroxide and a colour reaction with a quinonine dye (cholesterol reagent for Bayer RA1000 (Miles Inc, Diagnostic Division, Tarrytown, NY, USA)). HDL was separated by precipitation of other lipid fractions with phosphotungstic acid and magnesium chloride (Boehringer precipitating reagent). Triglyceride was measured by a colorimetric method using lipoprotein lipase and glycerol kinase (triglyceride kit for Bayer RA1000, see above). Interassay coefficients of variation were below 3% for all analyses across the measured ranges.

Data handling, analysis and definitions

Deaths were classified according to the International Classification of Disease (ICD) codes. Cardiovascular disease mortality is used to denote deaths from all circulatory diseases. Diagnosed CHD was defined from GP records as a record of myocardial infarction, angina, coronary revascularization procedure or positive treadmill test. Cerebrovascular disease was defined as a record of a stroke or transient ischaemic attack. Hypertension and diabetes were defined by being recorded in GP notes and hypercholesterolaemia was defined as a total cholesterol level $>7{\cdot}8$ mmol/l or treatment with a lipid-lowering agent. From questionnaire data CHD was defined as a positive response to 'Has a doctor ever told you that you have had a heart attack or angina?' and cerebrovascular disease was defined as a positive response to 'Has a doctor ever told you that you have had a stroke/mini-stroke or transient ischaemic attack?'. Diabetes, hypertension and hypercholesterolaemia were defined by positive responses to similar questions. Data on age at menarche and menopause, waist and hip circumferences,

ethnic origin, age at completion of education and family history were only available for questionnaire respondents. Age at menarche and menopause were self-reported. Hormone replacement therapy (HRT) use was defined as current use of any type of preparation. Reweighting by the inverse of the sampling fraction for categories of body mass index (BMI) ($<25\,kg/m^2$, $25–29{\cdot}9\,kg/m^2$, $>30\,kg/m^2$) was used to adjust for sampling bias in the clinical examination. Triglyceride values were logarithmically transformed, odds ratios were estimated using conditional logistic regression and analyses were performed using the Stata 5·0 package (Statacorp, TX, USA).

Results

Seven hundred and eighty-six women (76% of the original cohort) were traced by NHSCR, of whom 40 had emigrated and nine women were over 74 years of age. Cause of death and standardized mortality ratios for 70 cohort members who died before 31 March 1999 are given in Table 1. All-cause and cardiovascular disease mortality were not significantly different in cohort members from the general population but women with PCOS were significantly more likely to have diabetes as the underlying cause of death than women in the general population. A flow chart summarizing the follow-up process of the 678 traced, surviving cohort members resident in the United Kingdom below 75 years of age is given in Fig. 1. Health Authorities could not trace 17 women leaving 652 cohort members potentially available for morbidity follow-up. Permission was given by GPs to collect data from medical records for 155 of the 204 cohort members for whom baseline clinical data were missing (76%) and 403 age-matched women. Fifty-seven percent of GPs of cohort members agreed to take part in the questionnaire phase of the study. Response rate to the questionnaire was 72% for cohort members (257 replies) and 64% for control women (683 replies).

Data were collected from 345 cohort members (53% of eligible women): from GP records alone for 89 women, from questionnaires only for 191 women and from both GP records and questionnaires for 65 women. Twenty-six of the cohort members were excluded from the analysis because there was no history of oligomenorrhoea, acne, infertility or hirsutism. Data were collected on 1107 control women: 47 women (4·2%) reported 2 or more clinical features of PCOS as defined above and were excluded from the analysis. Consequently 319 women with PCOS and 1060 control women contributed to the analysis. Of the 319 cohort members for whom follow-up data were available 87% had microscopic evidence of polycystic ovary disease at diagnosis of PCOS.

Mean age of subjects was 56·7 (range 38–98) years. Average follow-up since diagnosis of PCOS for cohort members was 31 (range 15–47) years and the distribution of follow-up periods for cohort members is given in Table 2. Among women with PCOS, 46% reported hirsutism, 14% reported a history of acne, 77% reported irregular periods and 66% reported infertility. Age at menarche (13·5 *vs.* 12·8 years, $P<0{\cdot}001$) and at first pregnancy (27·0 *vs.* 24·3 years, $P<0{\cdot}001$) were higher in women with PCOS than control women but age at menopause was similar (47·5 *vs.* 47·6 years, $P=0{\cdot}9$). Ninety-nine percent of questionnaire respondents recorded their ethnic origin as white.

BMI and waist:hip ratio (WHR) were significantly higher in the PCOS group than in the control group, $27{\cdot}1$ *vs.* $26{\cdot}2\,kg/m^2$, $P<0{\cdot}01$ and 0·77 *vs.* 0·76, $P=0{\cdot}01$. Prevalence of cardiovascular disease and cardiovascular risk factors are given in Table 3. Odds ratios for CHD, cerebrovascular disease, diabetes, hypertension and high cholesterol levels are given in Table 4. Mean age at diagnosis of CHD, cerebrovascular disease, diabetes and hypertension did not differ between groups (data available from authors).

One hundred and twenty-four women (44% of those invited), 61 cohort members and 63 controls, attended the clinical examination. Prevalence of features of PCOS among cohort members did not differ between attenders and nonattenders for the clinical examination. Women in the PCOS group who attended for clinical examination were leaner than the whole group of questionnaire respondents with PCOS (mean BMI $24{\cdot}8$ *vs.* $27{\cdot}5\,kg/m^2$, $P<0{\cdot}001$). In the control group mean BMI in questionnaire respondents was similar for attenders and

Table 1 Numbers of deaths and standardized mortality ratios (SMR) for specific causes of death in LSHTM PCOS cohort to 31/03/99

Underlying cause of death	ICD code	No. of deaths	SMR (95% CI)
All causes	ICD-7/8/9 1–999	70	93 (72–117)
Cardiovascular disease	ICD-7400–468 & 330–334 ICD-8/9390–429	17	78 (45–124)
Coronary heart disease	ICD–7420 ICD-8/9410 –414	14	122 (67–205)
Cerebrovascular disease	ICD-7330–334 ICD-8/9430–438	2	35 (4–126)
Diabetes	ICD–7260 ICD-8/9250	4	460 (125–1177)

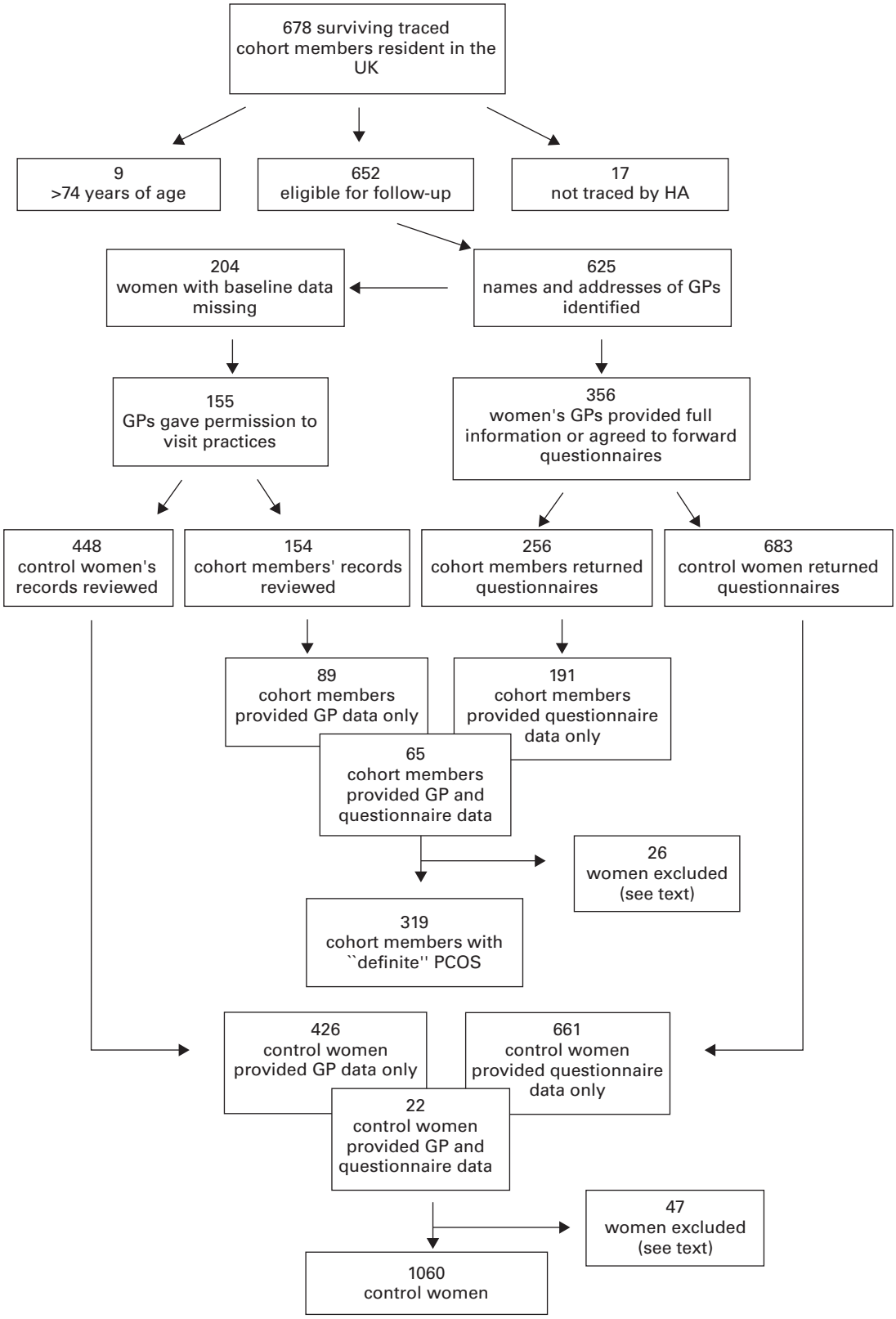

Fig. 1 Flow chart to show follow-up of London School of Hygiene & Tropical Medicine (LSHTM) cohort of women with PCOS.

Table 2 Follow-up since diagnosis of PCOS for 319 women with a history of PCOS in 5 years intervals

Follow-up (years)	<20	20–24	25–29	30–34	35–39	40–44	45–49	>50
N	2	8	87	144	62	9	3	4
%	1	3	27	45	19	3	1	1

nonattenders for the clinical examination: 25·6 *vs.* 25·8 kg/m^2, $P = 0{\cdot}8$. Prevalence of smoking, blood pressure, use of lipid-lowering or hormone replacement therapy and proportion of women with undiagnosed diabetes did not differ between cohort members and controls ($P > 0{\cdot}1$ for all variables). Other results of the clinical examination after reweighting by BMI category are given in Table 5. Self-reported measurements of weight, waist and hip circumferences were significantly lower than measurements taken at the clinical examination for both groups of women (by an average of 1·5 kg, 6 cm and 2 cm, respectively) but the discrepancies between self-reported and measured values did not differ significantly between PCOS and control groups.

Discussion

We have described the first long-term follow-up study of a large cohort of women with PCOS. Mortality and morbidity from diabetes and risk of nonfatal cerebrovascular disease were higher among women with PCOS. Increased morbidity from diabetes and hypertension in women with PCOS can be explained, in part, by the increased prevalence of obesity. It is interesting to note the increased prevalence of family history of diabetes among women with PCOS compared with controls and further studies are required to investigate the role of genetic and environmental factors in this association. Despite increased prevalence of several cardiovascular risk factors we found no significant excess of CHD mortality or morbidity among middle-aged women with PCOS. Although the confidence interval around the odds ratio for CHD morbidity is wide, it is sufficient to exclude an excess risk of three or more and suggests that the risk ratio of seven predicted by Dahlgren *et al*., 1992a is extremely unlikely.

No significant differences in socio-economic status, use of hormone replacement therapy, or smoking rates were found between PCOS and control groups suggesting that confounding

Table 3 Prevalence of CHD and CHD risk factors in 319 women with a history of PCOS and 1060 age-matched control women (see text for definitions)

	% (*n*)		
	PCOS group	Control group	*P*
CHD	4·7 (15)	4·0 (42)	0·6
Cerebrovascular disease	3·1 (10)	1·2 (13)	0·02
CHD and/or cerebrovascular disease	7·5 (24)	5·0 (53)	0·09
Diabetes	6·9 (22)	3·0 (32)	0·002
Diagnosed hypertension	23 (72)	19 (201)	0·2
Current smoker	20 (57)	20 (175)	0·98
Diagnosed high cholesterol	30 (51)	17 (84)	<0·001
BMI > 30 kg/m^2	26 (75)	18 (166)	<0·001
Post-menopausal status	81 (198)	82 (519)	0·7
Current HRT use	31 (94)	28 (262)	0·2
Husband in manual occupation	35 (71)	38 (188)	0·5
Family history of CHD	47 (115)	40 (254)	0·05
Family history of diabetes	27 (35)	17 (52)	0·02

Table 4 Odds ratios (OR) and 95% confidence intervals (95% CI) for CHD, stroke/TIA, diabetes, hypertension and high cholesterol for PCOS before and after adjusting for BMI

Outcome	Model	OR	95% CI	*P*
CHD	PCOS	1·5	0·7–2·9	0·3
	PCOS, BMI	1·2	0·5–2·6	0·7
Cerebrovascular disease	PCOS	2·8	1·1–7·1	0·03
	PCOS, BMI	3·4	1·2–9·6	0·02
CHD and/or cerebrovascular	PCOS	1·9	1·1–3·3	0·03
disease	PCOS, BMI	1·7	0·9–3·2	0·09
Diabetes	PCOS	2·8	1·5–5·5	0·002
	PCOS, BMI	2·2	0·9–5·2	0·08
Hypertension	PCOS	1·4	1·0–2·0	0·04
	PCOS, BMI	1·4	0·9–2·0	0·1
High cholesterol	PCOS	2·9	1·6–5·2	<0·001
PCOS, BMI	3·2	1·7–6·0	<0·001	

Table 5 Results of examination after reweighting to adjust for sampling fraction by BMI category (values are arithmetic means unless otherwise stated)

	PCO group	Control group	*P*
Body mass index (kg/m^2)	26·6	25·9	0·5
Waist:hip ratio	0·82	0·78	0·004
Mean systolic pressure (mmHg)	132	132	0·9
Mean diastolic pressure (mmHg)	79	82	0·2
Fasting glucose (mmol/l)	5·4	5·3	0·6
2 hour glucose (mmol/l)	6·3	5·9	0·4
Total cholesterol (mmol/l)	6·5	6·2	0·2
HDL cholesterol (mmol/l)	1·7	1·8	0·5
Triglycerides (mmol/l)*	1·4	1·1	0·02

* Geometric means and *P*-value for difference in mean values of natural logarithms are shown.

by these factors cannot explain the absence of excess CHD mortality or morbidity in the PCOS group. Just under a quarter of the original cohort members were not traced by ONS and it is possible that the mortality in this group of women may differ. Follow-up data were available for only approximately 50% of surviving traced cohort members but the similarity of baseline data between women who were followed up and the remainder of the cohort suggests that a representative sample was obtained. Our observation of a significant increase in risk of endometrial cancer (crude OR 5·3 (1·5–18·6), OR adjusted for BMI 6·1 (1·0–36·9)) based on seven affected women in the PCOS group provides validation of the diagnosis of PCOS in the study population.

Our results show that the unfavourable distribution of cardiovascular risk factors in women with PCOS compared with age-matched controls persists into middle-age. These findings are consistent with two smaller studies of middle-aged women with a history of PCOS (Dahlgren *et al*., 1992a; Talbott *et al*., 1995). Possible explanations for the discrepancy between prevalence of cardiovascular risk factors and expected prevalence of CHD could include inaccuracy of predictive models for CHD in women or presence of a protective factor against CHD in women with PCOS, such as prolonged exposure to unopposed oestrogen or elevated levels of vascular endothelial growth factor.

Most of the women in this cohort underwent laparoscopy, laparotomy or ovarian wedge resection for the diagnosis of PCOS to be made and they may represent women with more severe symptoms than those diagnosed today by ultrasound scanning. It has been suggested that women with PCOS and anovulatory cycles have higher prevalence of CHD risk factors than women with PCOS and ovulatory cycles (Conway *et al*., 1990; Robinson *et al*., 1993). Analysis of data collected from the subgroup of 249 women that we have followed up with evidence of anovulatory PCOS, as suggested by a history of irregular cycles, did not support this hypothesis (crude OR for CHD 1·0 (0·4–2·6), OR for CHD adjusted for BMI 0·8 (0·3–2·5)).

We conclude that, despite increased prevalence of diabetes and other cardiovascular risk factors in middle-age, risk of premature coronary heart disease in women with PCOS does not appear to be as high as previously predicted. Our results suggest that control of weight and blood pressure in women with PCOS are important to reduce their excess risk of diabetes and cerebrovascular disease. Elucidation of why women with PCOS appear to be protected from coronary heart disease would make a valuable contribution to understanding the aetiology of coronary heart disease.

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