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## Prognosis of angina with and without a diagnosis: 11 year follow up in the Whitehall II prospective cohort study

Harry Hemingway, Martin Shipley, Annie Britton, Michael Page, Peter Macfarlane, Michael Marmot



This is an abridged version; the full version is on [bmj.com](http://bmj.com)

### Abstract

**Objective** To investigate the prognosis of angina among people with and without diagnosis by a doctor and an abnormal cardiovascular test result.

**Design** Prospective cohort study with a median follow up of 11 years.

**Setting** 20 civil service departments originally located in London.

**Participants** 10 308 civil servants aged 35-55 years at baseline.

**Main outcome measures** Recurrent reports of angina; quality of life (SF-36 physical functioning); non-fatal myocardial infarction; death from any cause (n = 344).

**Results** 1158 (11.4%) participants developed angina, and 813 (70%) had no evidence of diagnosis by a doctor at the time of the initial report. Participants without a diagnosis had an increased risk of impaired physical functioning (age and sex adjusted odds ratio of 2.36 (95% confidence interval 1.91 to 2.90)) compared with those who had neither angina nor myocardial infarction throughout follow up. Among reported cases of angina without a diagnosis, the 15.5% with an abnormality on a study electrocardiogram had an increased risk of death (hazard ratio 2.37 (1.16 to 4.87)). These effects were similar in magnitude to those in participants with a diagnosis of angina.

**Conclusion** Undiagnosed angina was common and had an adverse impact on prognosis comparable to

that of diagnosed angina, particularly among people with electrocardiographic abnormalities. Efforts to improve prognosis among people with angina should take account of this submerged clinical iceberg.

### Introduction

People with angina do not necessarily seek medical care.<sup>1-3</sup> The size and prognosis of this group has not been assessed in a contemporary prospective cohort. Studies show that the combination of angina identified by questionnaire and an abnormality on a resting electrocardiogram identifies groups with increased risk of death.<sup>4 5</sup> Whether this risk is confined to patients who have sought medical care and have a diagnosis from a doctor (visible clinical iceberg) or if it extends to those without a diagnosis by a doctor (submerged clinical iceberg) is not known.<sup>6</sup>

Our objective was to investigate the prognosis of angina among people with and without a diagnosis by a doctor and an abnormal cardiovascular test result. We defined prognosis by four outcomes: death, myocardial infarction, recurrent reports of angina, and functional status.

### Methods

#### Participants

We invited all non-industrial civil servants aged 35-55 years working in 20 departments to participate in this study. The final cohort consisted of 10 308 participants

International Centre for Health and Society, Department of Epidemiology and Public Health, University College London Medical School, London WC1E 6BT

Harry Hemingway  
reader in clinical epidemiology  
Martin Shipley  
senior lecturer in medical statistics  
Annie Britton  
lecturer in epidemiology  
Michael Page  
research nurse  
Michael Marmot  
professor of epidemiology and public health

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Additional tables, figures, and questionnaire items appear on [bmj.com](http://bmj.com)

University of  
Glasgow,  
Department of  
Medical Cardiology,  
Royal Infirmary,  
Glasgow G3 7ER  
Peter Macfarlane  
professor of  
electrocardiology

Correspondence to:  
H Hemingway  
h.hemingway@  
public-health.ucl.ac.uk

(3413 women) with an overall response rate of 73%.<sup>7</sup> Participants completed questionnaires at five phases of data collection between 1985 and 1999 (fig A on bmj.com). At phase 5, 7830 participants completed a questionnaire (76% response rate from phase 1). At each phase we used the seven item Rose angina questionnaire to define angina independent of contact with medical care at each phase.<sup>8</sup>

#### Diagnosis of angina by a doctor

We obtained evidence of a diagnosis of angina from questionnaire items on diagnosis, investigation, and treatment (see bmj.com). We examined general practitioner and hospital records for diagnoses and abnormal test results among participants reporting positively to any of these questions. We also sought clinical records where the civil service gave a reason for absence as angina or myocardial infarction or when the spell of absence exceeded 21 days.

#### Abnormal test results

Regardless of contact with medical care, we investigated each participant with a resting 12 lead electrocardiogram at phases 1, 3, and 5. We defined abnormal results as Q waves, ST depression, inverted T waves, or left bundle branch block. Additionally, among participants who had sought medical care, we defined abnormal test results as the presence of one or more diseased vessels at coronary angiography or  $\geq 1$  mm ST depression on exercise electrocardiogram or a reversible defect on stress imaging.

#### Outcomes: classification of angina and recurrent reports

We classified angina according to evidence of diagnosis by a doctor and the presence of an abnormal test result and made chronological listings of each item of epidemiological and clinical record data. We coded pair-wise combinations of evidence in a hierarchy starting from a clinical record of diagnosis of angina plus an abnormal coronary angiogram at the top down to angina identified by the Rose angina questionnaire ("Rose angina") plus a normal study electrocardiogram at the bottom (see bmj.com). We assigned dated codes for each report of angina and defined a report of angina at each date that new evidence became available.

#### Outcomes: mortality, non-fatal myocardial infarction and physical functioning

Almost all (99.9%) participants were flagged at the NHS Central Registry, which notified us of dates of death. We defined non-fatal myocardial infarction by criteria of typical symptoms, enzyme abnormalities, and electrocardiographic changes.<sup>9</sup> We assessed physi-

cal functioning at phase 5 in 6839 participants by using the 10 item scale of the SF-36 health survey.<sup>10</sup>

#### Statistical analysis

We compared participants with four categories of angina, defined by the presence or absence of a diagnosis by a doctor or an abnormal test result, with participants who did not have angina or a myocardial infarction throughout follow up. We excluded from all analyses participants with angina or myocardial infarction before phase 1 and participants not flagged at the Central Registry.

We examined the prognosis of participants after their first report of angina by calculating the risk (probability) of specified events occurring in the next five years from their rate of occurrence. We calculated person years of survival by using the date of phase 1 and the dates of angina events and death or censoring at the end of 1999. We described the relation between types of angina and subsequent mortality with hazard ratios, and we used logistic regression to determine odds ratios of impaired physical functioning.

#### Results

A total of 1158 (11.4%) of 10 191 participants developed angina. We found 2772 reports of angina, so 1614 (58%) of angina reports were recurrent (see bmj.com).

*Recurrent angina and non-fatal myocardial infarction*—At the time of the first report of angina, 718/970 (74%) participants had no evidence of a diagnosis of angina by a doctor (see bmj.com). Of these, 470 (65%) reported angina again during follow up and remained without a diagnosis. Among participants with an abnormal test result, the absolute risk of non-fatal myocardial infarction was similar in those without a diagnosis by a doctor (15%) and those with a diagnosis (16%).

*Impaired physical functioning*—Participants with angina had an increased risk of impaired physical functioning at phase 5 (mean follow up seven years) compared with participants who did not have angina or myocardial infarction throughout follow up (table 1). The age and sex adjusted odds ratio was similar in participants without a diagnosis by a doctor and those with a diagnosis.

*Survival*—Mortality was increased in people with undiagnosed angina and an abnormal test result, compared with participants with neither angina nor myocardial infarction (table 2). Abnormal study electrocardiograms occurred in 268/1733 (15.5%) reported cases of undiagnosed angina. Among participants with a diagnosis by a doctor, we found some evidence for adverse survival in those with an abnormal test result.

#### Discussion

In this population based study, followed throughout the 1990s, more than half of people with angina had no evidence of diagnosis by a doctor. Among this group, an abnormal study electrocardiogram was common and was associated with worse survival. The increased risk of death and non-fatal myocardial infarction in people with angina and an abnormal test

**Table 1** Impaired physical functioning at phase 5 by type of first angina report

Type of first angina report	No of participants	No with poor physical functioning	Odds ratio (95% CI) adjusted for age and sex
No angina or myocardial infarction throughout follow up	6200	1374	1.00
Angina (diagnosis by doctor):			
Abnormal test (any)	53	24	2.29 (1.32 to 3.98)
No abnormal test	133	68	3.19 (2.25 to 4.53)
Angina (no diagnosis by doctor):			
Abnormal test (study electrocardiogram)	39	18	2.75 (1.45 to 5.22)
No abnormal test	414	169	2.36 (1.91 to 2.90)

**Table 2** All cause mortality by type of angina report

Type of angina report	No of participants†	No of deaths	Rate* per 1000 person years at risk	Hazard ratio* (95% CI)
No angina or myocardial infarction throughout follow up	8949	296	2.6	1.00
Angina (diagnosis by doctor):				
Abnormal test (any)	201	10	4.9	1.83 (0.95 to 3.52)
No abnormal test	231	5	2.4	0.90 (0.37 to 2.21)
Angina (no diagnosis by doctor):				
Abnormal test (study electrocardiogram)	150	8	6.0	2.37 (1.16 to 4.87)
No abnormal test	706	20	2.8	1.12 (0.71 to 1.78)

\*Adjusted for age and sex.

† No of participants contributing person years in each category of angina.

result was similar in magnitude in participants with and without a diagnosis. Recurrent reports of angina and impaired physical functioning were common in the undiagnosed group. The consistency of our findings across all four outcomes provides evidence for a prognostically important submerged clinical iceberg of people with angina.

### Angina without a diagnosis

No previous prospective studies during the 1990s have estimated the frequency and prognosis of angina without diagnosis by a doctor. Primary care consultations for angina rose between 1981 and 1991,<sup>11</sup> during a period of declining incidence of myocardial infarction. Most patients with symptoms of acute myocardial infarction seek medical care and obtain a diagnosis from a doctor. Our study shows that this is not true for angina. Our findings indicate that primary care disease registers, required by national policy,<sup>12</sup> are underestimating the burden of angina in the general population.

Several reasons exist for a lack of diagnosis. A person with angina may not seek medical care. Little is known about factors predicting this.<sup>3</sup> Once medical care has been sought, the doctor may miss or not record the diagnosis—a group that this study was not able to identify. If this were an important reason for the lack of diagnosis then this suggests a need for improvements in the diagnostic ability of clinicians.

### Prognosis of angina

A strength of our study lies in the repeated assessments of angina status made over prolonged follow up. An estimated 60% of the undiagnosed group reported angina again but remained without a diagnosis over five years of follow up.

Physical exercise is a common precipitant of angina. The presence of angina at baseline was associated with worse physical functioning at follow up. Importantly, this effect was similar in people with and without a diagnosis from a doctor and among both women and men.

We investigated all participants with resting electrocardiography and found adverse survival in people with angina without a diagnosis from a doctor in the presence of an abnormal resting electrocardiogram. This effect was similar in magnitude in those people with diagnosed angina who had an abnormal test result. Although many general practices have facilities for electrocardiography, the prognostic importance of common abnormalities is underappreciated.<sup>4</sup>

### Impact of medical care and policy implications

Guidelines in the United States and the United Kingdom recommend that all people with angina

### What is already known on this topic

Systematic identification and investigation of people with angina is recommended by government and professional bodies

Many people with angina do not seek medical care, but the size and prognosis of this group has not been prospectively investigated in a contemporary cohort

### What this study adds

Over half of participants with angina remained without a diagnosis on follow up

Physical functioning was impaired to a similar degree in people with and without a diagnosis of angina

Among people with an abnormal test result, the impact on mortality was similar in those with and without a diagnosis

should undergo resting electrocardiography in order to identify high risk groups for further investigation and treatment.<sup>12 13</sup> The cost effectiveness of systematic case finding (with questionnaire) and risk assessment (with electrocardiography) of people with angina in the general population awaits investigation.

### Conclusion

Among people with angina, a submerged clinical iceberg is associated with adverse prognosis across a range of outcomes. Reducing the population burden of angina requires consideration of people who have yet to be given a diagnosis.

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Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London WC1N 1EH  
 Elina Hyppönen research fellow  
 Chris Power professor of epidemiology and public health

Department of Social Medicine, University of Bristol, Bristol BS8 2PR

George Davey Smith professor of clinical epidemiology

Correspondence to: E Hyppönen [e.hypponen@ich.ucl.ac.uk](mailto:e.hypponen@ich.ucl.ac.uk)

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## Effects of grandmothers' smoking in pregnancy on birth weight: intergenerational cohort study

Elina Hyppönen, George Davey Smith, Chris Power

### Abstract

**Objective** To investigate the influences on birth weight of maternal smoking during pregnancy across generations.

**Design** Intergenerational cohort study.

**Participants** Members of the 1958 birth cohort and their offspring and mothers.

**Setting** England, Scotland, and Wales.

**Main outcome measure** Birth weight.

**Results** Information on grandmothers' smoking during pregnancy was available for 9028 singleton offspring of 4302 female cohort members. Assuming heritable transmission through the intergenerational birth weight association, grandmothers' smoking was predicted to result in a 34 g reduction (95% confidence interval -41 g to -28 g) in the birth weight of grandchildren. Random effects models showed a negative association between grandmothers' smoking and birth weight of grandchildren ( $\beta$  regression coefficient -24 g, -50 g to 3 g), but this effect was eliminated after adjustment for maternal smoking (0 g, -26 g to 26 g). No association was evident among the offspring of non-smoking mothers ( $n=6105$ ; 14 g, -17 g to 46 g), and after adjustment for maternal birth weight and height and body mass index as adults, grandmothers' smoking was positively associated with the birth weight of grandchildren (45 g, 10 g to 80 g).

**Conclusion** Deficits in mothers' birth weight attributable to their mother smoking was not evident in the grandchildren.

### Introduction

Evidence on the effects of exposure of fetuses to tobacco smoke has been restricted to two generations

(parent and offspring), but there are reasons to expect that the effects of maternal smoking during pregnancy could extend to the third generation. The Dutch hunger winter study showed that the effects of famine during fetal life may be transmitted to subsequent generations through an intergenerational association.<sup>1</sup> Evidence to support regulation of fetal development by an intrauterine mechanism has been obtained from multigenerational studies in rhesus monkeys.<sup>2</sup> The deleterious effect of maternal smoking on stature of offspring and risk of obesity in offspring also suggests effects across generations.<sup>3,4</sup> We investigated whether maternal smoking during pregnancy reduces the birth weight of infants across more than one generation.

### Participants and methods

We used data from the 1958 birth cohort.<sup>5</sup> The cohort consisted of 16 751 live births in England, Scotland, and Wales.<sup>6</sup> Detailed information was collected at birth (98% of cohort members) and at ages 7, 11, 16, 23, 33, and 41.<sup>7</sup> Birth data were largely collected by midwives for cohort members, supplemented with obstetric records and interviews.<sup>6</sup> Information on smoking before and during the pregnancy was reported by the mothers of cohort members in 1958 and coded as smoking up to or after the fourth month of pregnancy. At age 33 and 41, cohort members provided data on their own offspring (birth weight, length of gestation). They were asked if they had smoked during pregnancy, reported as not at all or up to or after the fifth month of pregnancy. Height of cohort members was measured at age 33, supplemented with self reported values from surveys held at ages 23 and 41. We used the weight of cohort members at age 23.