Supplementary notes on Methods

The Whitehall II study originally comprised 10,308 (3413 women) individuals who, at recruitment in 1985/8, were London-based government employees (civil servants) aged 35 to 55 years.[1] An on-going study, follow-up clinical examinations have taken place approximately every 5 or 6 years in 1991/93, 1997/99, 2002/04, 2007/9, and 2012/13. The study was approved by the University College London ethics committee and all participants provided written consent.

The methods used in the Whitehall II study have been described elsewhere.[1;2] In brief, members self-reported current cigarette smoking, physical activity, alcohol intake, and parental history of death from heart attack, stroke, or other heart condition. Biological measurements were made by trained research nurses following standard operating procedures. Blood glucose was measured using the glucose oxidase method with diabetes defined by the World Health Organization (WHO) 1999 criteria based on fasting glucose ≥7.0 mmol/l or 2-h glucose ≥11.1 mmol/l. Participants reporting doctor diagnosed diabetes or use of diabetes medication were classified as having diabetes regardless of their oral glucose tolerance test results. Height and weight were measured directly and body mass index (BMI) computed using the usual formulae (weight[kg]/height^2[m^2]). Systolic and diastolic blood pressures were measured twice in the sitting position after 5 minutes of rest with the average of the 2 readings used in the present analyses. Blood samples, taken after at least 5 hours of fasting, were used to measure levels total and HDL cholesterol and insulin.

Comparator studies

Described in detail elsewhere,[3] the BRHS is an on-going prospective study of cardiovascular disease involving men aged 40–59 years at enrolment who were selected from general

medical practices in each of 24 towns in England, Wales, and Scotland in 1978/80. Each man completed a standard questionnaire administered by the research nurses and provided a series of clinical measurements. After excluding study members with prevalent coronary heart disease (CHD) at baseline, the resulting sample, featured herein, comprised 7198 men.[4]

The design of the original Framingham Heart Study[5] and the Framingham Offspring Study[6] have also been detailed previously. Participants included in the present comparison[7] attended the 11th biennial examination cycle of the original cohort (1968/71), or the first (1971/75) or third (1984/87) examination cycles of the Offspring cohort. After excluding study members with prevalent CVD, the resulting sample of 8491 participants (4522 women) was 30-74 years of age. As in the BRHS, data were collected using a combination of questionnaire and clinical measurements.

Wherever possible in our analyses of Whitehall II study raw data we replicated published analyses from the BRHS[4] and the Framingham study.[6] The characteristics matched in the analysis included the categorisation of risk factors, the type of endpoint (CHD in the BRHS [see table 2[4]], CVD in Framingham [see table 2[6]]), the duration of follow-up (15 years in the BRHS, 12 in Framingham), the age-range of study members (40-59 years in the BRHS, 30-74 years in Framingham), and the statistical adjustments made to the effect estimates. For the BRHS comparison, we used data collected in Whitehall II study members in 1991/93 as our baseline with follow-up for non-fatal and fatal CHD until 2007/09; for the Framingham comparison, the comparable data collection phase was 1991/3 with follow-up for fatal and non-fatal CVD until 2002/4.

As the participants in the BRHS were men free of prevalent CHD,[4] Whitehall II analyses was similarly restricted to this group. Prevalent CHD was defined as a history of myocardial infarction/angina identified via the WHO chest pain questionnaire together with corroboration by any one of the following sources: medical records, or abnormalities in a resting electrocardiogram, exercise electrocardiogram, or a coronary angiogram. In accordance with BRHS, among the included men, 'pre-existing CHD' was defined as having a history of angina/possible myocardial infarction, or only electrocardiographic evidence of possible or definite myocardial ischaemia.[4] In these analyses, the outcome of interest was CHD as denoted by death with CHD cited as the underlying cause (International Classification of Diseases ninth (ICD-9[8]) revision codes 410 to 414; ICD-10[9] codes I20 to I25), or a non-fatal CHD event (myocardial infarction/heart attack).

For comparison with Framingham results,[6] Whitehall II study members with prevalent CHD or stroke[10] were excluded from analyses. The outcome of interest was CVD, denoted by any of the following: death with CHD (defined above) or stroke (ICD-9: 430 to 438, ICD-10: I60 to I69) as the underlying cause; or non-fatal CHD (defined above plus angina), stroke or heart failure as obtained through national Hospital Episode Statistics data.

Statistical analyses

In the analyses of Whitehall II data, hazard ratios (HRs) with accompanying 95% confidence intervals (CIs) were computed using Cox's proportional hazards regression model[11] with follow-up time as the underlying time scale. Censoring was made at date of disease endpoint, date at loss to follow-up, or date at end of follow-up (comparison dependent); whichever came first.

While the published risk factor–coronary heart disease relations in the BRHS were presented in conventional fashion, the hazard ratios for the continuous variables in the Framingham study[6] have been calculated from log-transformed results. For the continuous variables, the hazard ratios and confidence intervals associated with a 20% increase in the risk factor have been calculated using the formula, $HR = FHR^{\ln(1.2)}$, where FHR is the published Framingham hazard ratio. The categorical risk factors–CVD associations were computed conventionally. The Framingham results were stratified by gender; we therefore did the same in the Whitehall study (men only were sampled in the BRHS). A p-value summarising any statistical difference in hazard ratios between studies was computed by testing the difference between the log hazard ratios. The standard error of the log hazard ratios for the BRHS and Framingham study were computed from the reported hazard ratio confidence intervals.

References

(1) Marmot MG, Davey-Smith G, Stansfeld S, Patel C, North F, Head J et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet* 1991; 337(8754):1387-1393.

(2) Marmot M, Brunner E. Cohort Profile: the Whitehall II study. *Int J Epidemiol* 2005; 34(2):251-256.

(3) Walker M, Whincup PH, Shaper AG. The British Regional Heart Study 1975-2004. *Int J Epidemiol* 2004; 33(6):1185-1192.

(4) Wannamethee SG, Shaper AG, Whincup PH, Walker M. Role of risk factors for major coronary heart disease events with increasing length of follow-up. *Heart* 1999; 81:374-379.

(5) Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health* 1951; 41(3):279-281.

(6) Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol* 1979; 110(3):281-290.

(7) D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; 117(6):743-753.

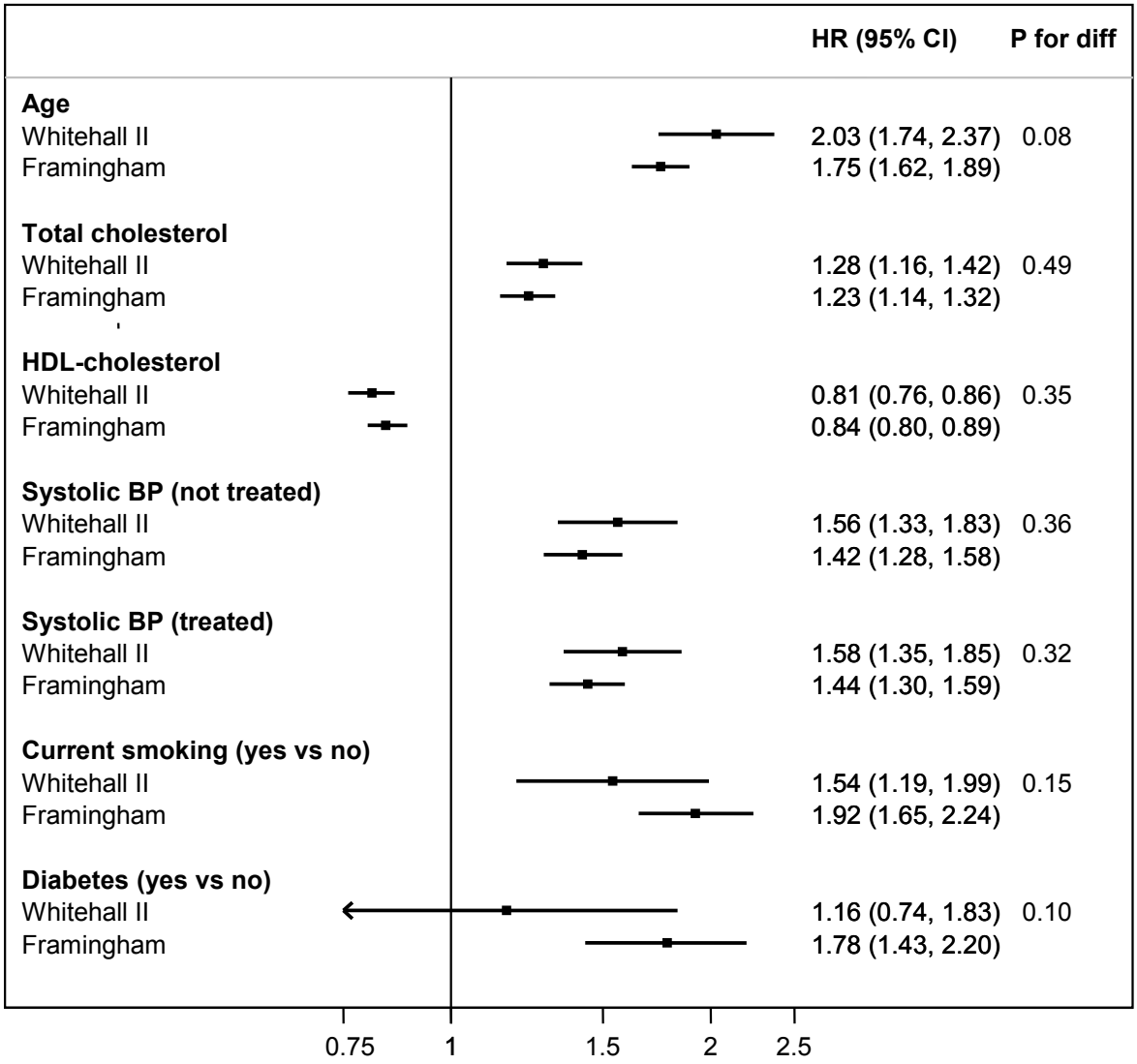
(8) Anon. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ninth revision). Geneva: WHO; 1977.

(9) Anon. Classification of diseases. 10th revision. Copenhagen: Danish National Board of Health; 1993.

(10) Britton A, Milne B, Butler T, Sanchez-Galvez A, Shipley M, Rudd A et al. Validating self-reported strokes in a longitudinal UK cohort study (Whitehall II): Extracting information from hospital medical records versus the Hospital Episode Statistics database. *BMC Med Res Methodol* 2012; 12:83.

(11) Cox DR. Regression models and life-tables. *J R Stat Soc [Ser B]* 1972; 34:187-220.

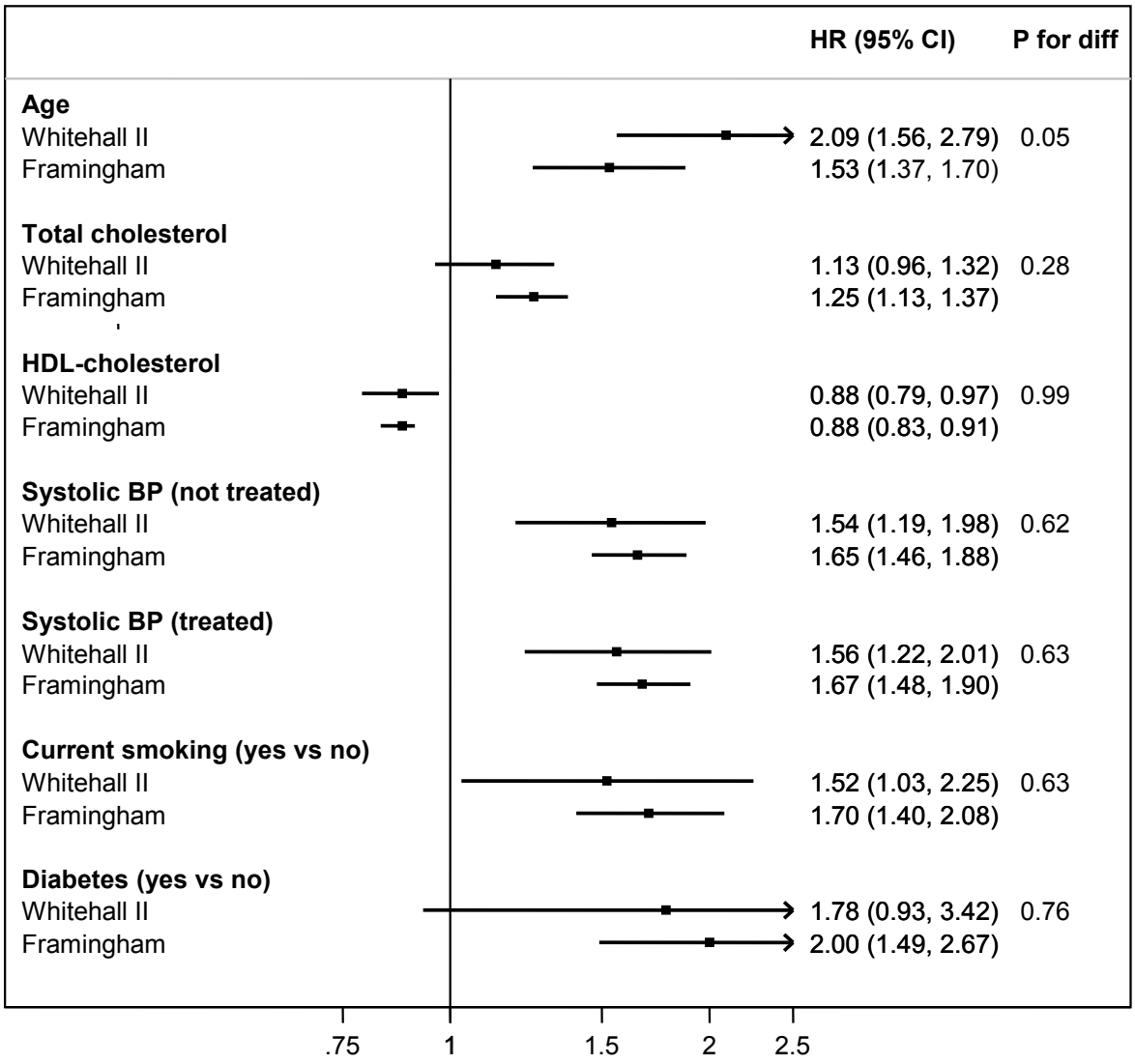
Supplementary Figure 1a. Classic risk factors for coronary heart disease: the Whitehall II study and the Framingham study - men



Analyses are based on 3969 men (718 CVD events) in the Framingham study and 5042 men (447 CVD events) in the Whitehall II study. Results are hazard ratios (95% confidence intervals). For the continuous variables, the hazard ratios are for a 20% increase in the risk factor. Effect estimates are mutually adjusted.

The hazard ratios for the continuous variables in the Framingham study have been calculated from log-transformed results. For the continuous variables, the hazard ratios and confidence intervals associated with a 20% increase in the risk factor have been calculated using the formula, $HR = FHR^{\ln(1.2)}$, where FHR is the published Framingham hazard ratio.

Supplementary Figure 2b. Classic risk factors for coronary heart disease: the Whitehall II study and the Framingham study - women



Analyses are based on 4522 women (456 CVD events) in the Framingham study and 2248 men (162 CVD events) in the Whitehall II study. Results are hazard ratios (95% confidence intervals). For the continuous variables, the hazard ratios are for a 20% increase in the risk factor. Effect estimates are mutually adjusted.

The hazard ratios for the continuous variables in the Framingham study have been calculated from log-transformed results. For the continuous variables, the hazard ratios and confidence intervals associated with a 20% increase in the risk factor have been calculated using the formula, $HR = FHR^{\ln(1.2)}$, where FHR is the published Framingham hazard ratio.