**Peripheral arterial disease prevalence model for small populations:**

**Technical Document produced for Public Health England**

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Peripheral arterial disease prevalence model Technical Document

# Executive Summary

# Background

The Department of Primary Care & Public Health (PCPH) in the School of Public Health (SPH) at Imperial College London (ICL) has tendered successfully to Public Health England (PHE) to develop small population prevalence models for several chronic diseases. PHE has requested a single cardiovascular disease (CVD) prevalence model. CVD is a term used to define disorders which affect the heart and blood vessels. These may be broadly subcategorised into two classes: 1) atherosclerotic CVDs including coronary heart disease (CHD), cerebrovascular disease more commonly called stroke, and transient ischaemic attacks (TIAs), and peripheral arterial disease (PAD); and 2) CVDs of other aetiology including congenital and rheumatic heart disease and cardiac arrhythmias. We considered that it would be feasible, and more useful at the local level, to develop three separate prevalence models for CHD, stroke and TIA, and PAD, nevertheless using the same data source and exactly the same methods. There is a large but not complete overlap in risk factors for the three diseases, but the prevalence of each is distinct. The prevalence of each disease in each local population can be summed to provide an overall prevalence of CVD. (For the present models, we focus on the atherosclerotic CVDs (CHD, CD/stroke, and PAD) as these represent the vast majority of the CVD disease burden in the UK.) This Technical Document considers all CVD risk factors, but then describes the derivation of the model for CHD.

Collectively, CVD is the leading cause of mortality worldwide, accounting for 17.5 million deaths in 2012.[1] In the UK, CVD remains among the leading causes of death and presents a tremendous financial burden, with the National Health Service (NHS) having spent £6.8 billion on CVD treatment in 2012/13.[2] The prominent risk factors for CVD are well established. While many of these cannot be altered (e.g. age, gender, family history) there are numerous examples of modifiable risk factors including smoking, alcohol consumption and obesity. These represent targets for primary prevention strategies which can significantly reduce the risk of an individual developing CVD.

## CVD Risk Factors

A non-systematic literature search was conducted for known CVD risk factors. These are shown in the following table, with associated references (Table 1):

Table 1: CVD risk factor list

| Risk factor | References |
| --- | --- |
| Age | [3] [4-8] |
| Gender | [9-20] [21] |
| Ethnicity | [22 23] [24 25] [26-28] |
| Smoking | [7] |
| Diabetes | [7 8 11 29-32] |
| Hypertension | [7] |
| Dyslipidaemia | [33-35] |
| Obesity |  |
| Physical activity |  |
| Family history |  |
| Socioeconomic status | [36 37] |
| Previous stroke/TIA |  |
| Atrial fibrillation |  |
| Inflammatory markers |  |
| Hyperviscosity/Hypercoagulable state |  |
| Hyperchromocysteinaemia |  |
| Chronic renal insufficiency |  |

### Age

Age is the most significant non-modifiable risk factor for developing cardiovascular disease. Data from the WHO and UN suggest that the risk of mortality from ischaemic heart disease triples with each decade of life (2.3-2.7-fold increase per decade for men, 2.9-3.7 for women).[3] Similar gradients are seen in carotid disease and PAD,[4-8] with risk of developing these conditions increasing exponentially with age. The mechanisms for this are debatable, but may include diminishing structural and mechanical integrity of the heart and blood vessels as well as the increased risk of exposure to other common risk factors.

### Gender

Men are at higher risk of developing CVD than women, although the risk for women increases substantially after menopause.[9-20] Over time and at different ages, independent of diagnostic and treatment practices, women have a similar or slightly higher prevalence of angina than men across countries with widely differing myocardial infarction mortality rates.[19] There are also gender-specific differences in the effects of other risk factors. Guideline-recommended treatments for angina are underused in women and older patients.[21] These suboptimal practice patterns, which are worst in older women, are of particular concern. The prevalence of minor ECG changes is slightly higher among men (10.4%v 9.5% in women). The occurrence of ischaemia-like findings on the ECG was comparable between men and women (9.0% v 9.8%).[20]

### Ethnicity

Migrants of South Asian descent worldwide have elevated risks of morbid and mortal events because of ischaemic heart disease.[22 23] In the UK, mortality from IHD in both South Asian men and women is 1.5 times that of the general population, and South Asians have not benefited to the same extent from the general decline in deaths caused by IHD over the last few decades.[24 25] Declines in stroke incidence have been observed the UK in men, women, White groups, and those aged >45 years, but not in Black groups. The reduction in prevalence of before-stroke risk factors was mostly seen in White patients aged >55 years, whereas an increase in diabetes mellitus was observed in younger Black patients.[26 27] Incidence rates of first ever stroke adjusted for age and sex are twice as high in Black people compared with White people. This excess incidence cannot be accounted for by differences in social class in ages 35-64. Black people tend to have their first stroke at a younger age than White people. The excess incidence is found in all pathological types of stroke but is greatest for primary intracerebral haemorrhage.[28]

### Hypertension

Hypertension ranks among the most significant risk factors for cardiovascular disease. Willey et al. estimated hypertension to account for almost one quarter of the population risk of CVD (population attributable risk (PAR) = 24.3%, 95% CI 13.2-35.4%).[29] Severe hypertension (systolic blood pressure, SBP≥160mm Hg) has been associated with a two-fold increase in risk of CHD.[38] The risk among pre-hypertensive individuals (BP 120-139/80-89 mm Hg) is debatable, with different studies drawing different conclusions. However, Huang et al. recently performed a meta-analysis including over 500,000 individuals from 17 studies and demonstrated a significant association of pre-hypertension with risk of CHD (RR 1.43, 95% CI 1.26-1.63).[25] Hypertension has a stronger association with stroke, with PAR estimates as high as 36%.[5] Sun et al. showed an increased risk of stroke across several different categories of hypertension, with combined systolic and diastolic hypertension presenting the greatest risk (OR 2.13, 95% CI 1.78-2.75). Similarly for PAD, Fowkes et al. calculated an odds ratio of 1.47 (95% CI 1.37-1.57) among hypertensive patients (BP ≥ 140/90 mm Hg) compared to normotensive subjects.[7]

### Smoking

Smoking has long been established as a risk factor for CHD, and represents perhaps the most easily modifiable risk factor for CVD. In ranking the major risk factors for coronary heart disease, Schnohr et al. determined that smoking was the most important risk factor for women (OR 1.74, 95% CI 1.43-2.11) and the fifth most important for men (OR 1.62, 95% CI 1.25-2.09) when comparing non-smokers to individuals smoking >15g of tobacco per day.[38] Similarly, Tolstrup et al. showed a significant correlation between the amount of tobacco smoked and the odds of developing coronary heart disease in a pooled analysis, and that the risk was higher for women than in men.[39] Furthermore, there is ample evidence suggesting that cessation of smoking greatly reduces the risk of developing CHD.[40] Similar associations are seen in stroke, with Peters et al. reporting an 83% increased risk of stroke among women who currently smoke compared to those who have never smoked, and 67% increase among men.[13] There is an approximate two-fold increase in the risk of PAD for both current smokers (OR 2.09, 95% CI 1.91-2.29) and former smokers (OR 1.87, 95% CI 1.64-2.18) compared to non-smokers.[7]

### Diabetes

Diabetes is associated with a 2 to 4-fold increase in the risk of developing CVD.[7 8 11 29-32] While this association may be somewhat confounded by the fact that diabetes is linked to several other CVD risk factors (e.g. obesity, hypertension, dyslipidaemia), there is evidence to suggest that diabetes is an independent risk factor. There is a graded positive association between HbA1c levels and risk of CHD, which holds true after adjustment for blood pressure, BMI and blood lipids, suggesting that poor blood glucose control increases risk of CHD.[41] (Zhao et al. 2014). Yusuf et al. estimated the odds of an individual with diabetes having a heart attack are 2.37 times greater (99% CI 2.07-2.71) than a non-diabetic when adjusting for other factors.[31]

The risk for stroke is similarly elevated, as studies show an approximately two-fold increase in the risk of stroke in diabetics compared to non-diabetics. Data from the Clinical Practice Research Datalink (CPRD) in the UK and estimated an odds ratio 2.19 (95% CI 2.09-2.32).[42] Peters et al. determined a similar risk in a recent meta-analysis, while noting an increased risk in women compared to men (OR 2.28, 95% CI 1.93-2.69 vs. 1.83, 95% CI 1.60-2.08).[12] Diabetes is also a key risk factor for PAD. Estimates range from 10-40% for the prevalence of PAD among individuals with diabetes, and PAD is the leading cause of amputation in diabetics.[43] Fowkes et al. showed a 68% increased risk of PAD among diabetic subjects in their meta-analysis (OR 1.68, 95% CI 1.53-1.84).[7]

### Obesity

We are now beginning to understand the underlying mechanisms as well as the ways in which smoking and dyslipidaemia increase, and physical activity attenuates, the adverse effects of obesity on cardiovascular health.Obesity is associated with other risk factors – diabetes, dyslipidaemia etc- which may mediate its effect on CVD. [44] Adipose tissue releases a large number of bioactive mediators that influence not only body weight homeostasis but also insulin resistance - the core feature of type 2 diabetes - as well as alterations in lipids, blood pressure, coagulation, fibrinolysis and inflammation, leading to endothelial dysfunction and atherosclerosis.[45] Body mass index (BMI) shows a positive association with cerebrovascular risk which is non-significant after adjustment for physical inactivity, smoking, hypertension, and diabetes (odds ratio 1.18; 95% CI, 0.77 to 1.79).[46] Markers of abdominal adiposity are strongly associated with the risk of stroke/TIA. For the waist-to-hip ratio, adjusted odds ratios for every successive tertile were greater than that of the previous one.

### Dyslipidaemia

High total cholesterol, low high density lipoproteins (HDL), and high low density lipoproteins (LDL) are all well-established CVD risk factors and are included in both the Framingham and QRISK2 CVD risk scores.[33-35]

### Deprivation and socioeconomic status

In the UK material deprivation is a well-established CVD risk factor and is included in the QRISK2 CVD risk score.[36 37] Favourable population-wide trends in smoking, blood pressure and cholesterol are consistent with falling CHD death rates. However, adverse trends in obesity and diabetes in deprived populations are likely to counteract some of these gains. Furthermore, little progress over the last 15 years has been made towards reducing risk factor inequalities.[47] Approximately half the recent CHD mortality fall in England is attributable to improved treatment uptake. This benefit occurred evenly across all social groups. However, the opposing trends in major risk factors means that their net contribution amounted to just over a third of the CHD deaths averted; and these also varied substantially by socioeconomic group.[48]

### Physical Activity

In a recent meta-analysis, compared with individuals reporting no leisure time physical activity, there was a 20% lower overall mortality risk among those performing more than the recommended minimum, a 31% lower risk at 1 to 2 times the recommended minimum, and a 37% lower risk at 2 to 3 times the minimum. A similar dose-response relationship was observed for mortality due to CVD.[49] Sedentary time is independent of physical activity associated with an increased risk of diabetes, CVD and CVD mortality.[50] Compared with inactive individuals, those who exercise for an average of 15 min a day have a 14% reduced risk of all-cause mortality, and a 3 year longer life expectancy.[51].

### Inflammatory Markers

Although there is a growing evidence base showing the importance of other inflammatory marker data, [52] they are either not available in the national data sources available for use, or (more commonly) data are not available for small local populations, so we have not considered them further here.

### Chronic Kidney Disease

Chronic kidney disease (CKD) is associated with a number of other CVD risk factors, notably hypertension and diabetes, which contribute to the increased risk of CVD observed in CKD patients. However CKD has been shown to be an independent risk factor for CVD after adjustment for these related factors.[53] There is a relative risk of 1.4 (95% CI 1.3-1.5) for CHD development in individuals with CKD.[54] The data on stroke is somewhat less clear, with different studies arriving at dissimilar conclusions on the independence of CKD as a risk factor.[55] However in a large meta-analysis, Lee et al. showed a statistically significant 43% increase in risk of stroke among patients with a glomerular filtration rate (eGFR) < 60 mL/min/1.73m2 (RR 1.43, 95% CI 1.31-1.57), which held even after adjustment for traditional risk factors.[56] CKD is an established risk factor for PAD, with a two-fold increase in odds of developing PAD among patients with an eGFR < 60 mL/min/1.73m2 (OR 2.0, 95% CI 1.4-2.7).[6]

Table 2 summarises all the CHD risk factors we reviewed with their recent pooled, matched or adjusted odds ratios.

Table 2: CVD risk factors with their pooled, matched or adjusted odds ratios

| Risk factor | Type of Odds Ratio & references | Odds Ratio | 95% CI | Effect on Outcome |
| --- | --- | --- | --- | --- |
| Hypertension | HR (adjusted)[38] |  |  |  |
| SBP<120 mm Hg |  | 1.00 |  | Reference |
| SBP 120-139 mm Hg |  | 1.32 | [0.96-1.82] | NS |
| SBP 140-159 mm Hg |  | 1.63 | [1.18-2.24] | Risk Factor |
| SBP≥160 mm Hg or BP medication |  | 2.07 | [1.48-2.88] | Risk Factor |
|  |  |  |  |  |
| Smoking | HR (adjusted)[38] |  |  |  |
| Never smoker |  | 1.00 |  | Reference |
| Former smoker |  | 1.52 | [1.18-1.97] | Risk Factor |
| 1-4g tobacco/day |  | 1.63 | [0.91-2.94] | NS |
| 5-14g tobacco/day |  | 1.46 | [1.09-1.95] | Risk Factor |
| ≥15g tobacco/day |  | 1.62 | [1.25-2.09] | Risk Factor |
|  |  |  |  |  |
| Diabetes | For risk of MI – adjusted for all other risk factors[31] |  |  |  |
| No |  | 1.00 |  | Reference |
| Yes |  | 2.37 | [2.07-2.71] (99% CI) | Risk Factor |
| Total cholesterol | HR (adjusted)[38] |  |  |  |
| 1st quartile |  | 1.00 |  | Reference |
| 2nd quartile |  | 1.09 | [0.88-1.35] | NS |
| 3rd quartile |  | 1.18 | [0.95-1.46] | NS |
| 4th quartile |  | 1.77 | [1.42-2.21] | Risk Factor |
| HDL cholesterol | HR (adjusted)[38] |  |  |  |
| ≥1.5 mmol/L |  | 1.00 |  | Reference |
| 1.0-1.4 mmol/L |  | 1.39 | [1.18-1.64] | Risk Factor |
| <1.0 mmol/L |  | 1.65 | [1.30-2.09] | Risk Factor |
| Family history | HR (adjusted)[38] |  |  |  |
| No |  | 1.00 |  | Reference |
| Yes |  | 1.49 | [1.04-2.14] | Risk Factor |
| Physical activity | HR (adjusted)[38] |  |  |  |
| High activity in leisure time |  | 1.00 |  | Reference |
| Moderate activity in leisure time |  | 1.00 | [0.85-1.18] | NS |
| Low activity in leisure time |  | 1.30 | [1.03-1.65] | Risk Factor |
| Obesity | RR (adjusted) |  |  |  |
| BMI 18.5-22.9 (Men) |  | 1.00 |  | Reference |
| BMI 23.0-24.9 (Men) |  | 1.22 | [1.04-1.43] | Risk Factor |
| BMI 25.0-26.9 (Men) |  | 1.53 | [1.31-1.78] | Risk Factor |
| BMI 27.0-29.9 (Men) |  | 1.71 | [1.44-2.02] | Risk Factor |
| BMI 30+ (Men) |  | 1.81 | [1.48-2.22] | Risk Factor |
| BMI 18.5-22.9 (Women) |  | 1.00 |  | Reference |
| BMI 23.0-24.9 (Women) |  | 1.10 | [0.93-1.30] | NS |
| BMI 25.0-26.9 (Women) |  | 1.34 | [1.11-1.61] | Risk Factor |
| BMI 27.0-29.9 (Women) |  | 1.53 | [1.27-1.84] | Risk Factor |
| BMI 30+ (Women) |  | 2.16 | [1.81-2.58] | Risk Factor |
| Inflammatory Markers |  |  |  |  |
| IL-6 | HR per 1-SD increase (adjusted)[57] | 1.46 | [1.30-1.64] | Risk Factor |
| CRP | RR per 3-fold increase (adjusted) (Emerging risk factors collaboration – 2010)[52] | 1.64 | [1.54-1.75] | Risk Factor |
| Chronic Kidney Disease | Relative rate (adjusted)[54] | 1.4 | [1.3-1.5] | Risk Factor |
| Risk factor | Type of Odds Ratio & references | Odds Ratio | 95% CI | Effect on Outcome |
| Hypertension | HR (adjusted)[38] |  |  |  |
| SBP<120 mm Hg |  | 1.00 |  | Reference |
| SBP 120-139 mm Hg |  | 1.32 | [0.96-1.82] | NS |
| SBP 140-159 mm Hg |  | 1.63 | [1.18-2.24] | Risk Factor |
| SBP≥160 mm Hg or BP medication |  | 2.07 | [1.48-2.88] | Risk Factor |
|  |  |  |  |  |
| Smoking | HR (adjusted)[38] |  |  |  |
| Never smoker |  | 1.00 |  | Reference |
| Former smoker |  | 1.52 | [1.18-1.97] | Risk Factor |
| 1-4g tobacco/day |  | 1.63 | [0.91-2.94] | NS |
| 5-14g tobacco/day |  | 1.46 | [1.09-1.95] | Risk Factor |
| ≥15g tobacco/day |  | 1.62 | [1.25-2.09] | Risk Factor |
|  |  |  |  |  |
| Diabetes | For risk of MI – adjusted for all other risk factors[31] |  |  |  |
| No |  | 1.00 |  | Reference |
| Yes |  | 2.37 | [2.07-2.71] (99% CI) | Risk Factor |
| Total cholesterol | HR (adjusted)[38] |  |  |  |
| 1st quartile |  | 1.00 |  | Reference |
| 2nd quartile |  | 1.09 | [0.88-1.35] | NS |
| 3rd quartile |  | 1.18 | [0.95-1.46] | NS |
| 4th quartile |  | 1.77 | [1.42-2.21] | Risk Factor |
| HDL cholesterol | HR (adjusted)[38] |  |  |  |
| ≥1.5 mmol/L |  | 1.00 |  | Reference |
| 1.0-1.4 mmol/L |  | 1.39 | [1.18-1.64] | Risk Factor |
| <1.0 mmol/L |  | 1.65 | [1.30-2.09] | Risk Factor |
| Family history | HR (adjusted)[38] |  |  |  |
| No |  | 1.00 |  | Reference |
| Yes |  | 1.49 | [1.04-2.14] | Risk Factor |
| Physical activity | HR (adjusted)[38] |  |  |  |
| High activity in leisure time |  | 1.00 |  | Reference |
| Moderate activity in leisure time |  | 1.00 | [0.85-1.18] | NS |
| Low activity in leisure time |  | 1.30 | [1.03-1.65] | Risk Factor |
| Obesity | RR (adjusted) |  |  |  |
| BMI 18.5-22.9 (Men) |  | 1.00 |  | Reference |
| BMI 23.0-24.9 (Men) |  | 1.22 | [1.04-1.43] | Risk Factor |
| BMI 25.0-26.9 (Men) |  | 1.53 | [1.31-1.78] | Risk Factor |
| BMI 27.0-29.9 (Men) |  | 1.71 | [1.44-2.02] | Risk Factor |
| BMI 30+ (Men) |  | 1.81 | [1.48-2.22] | Risk Factor |
| BMI 18.5-22.9 (Women) |  | 1.00 |  | Reference |
| BMI 23.0-24.9 (Women) |  | 1.10 | [0.93-1.30] | NS |
| BMI 25.0-26.9 (Women) |  | 1.34 | [1.11-1.61] | Risk Factor |
| BMI 27.0-29.9 (Women) |  | 1.53 | [1.27-1.84] | Risk Factor |
| BMI 30+ (Women) |  | 2.16 | [1.81-2.58] | Risk Factor |
| Inflammatory Markers |  |  |  |  |
| IL-6 | HR per 1-SD increase (adjusted)[57] | 1.46 | [1.30-1.64] | Risk Factor |
| CRP | RR per 3-fold increase (adjusted)[52] | 1.64 | [1.54-1.75] | Risk Factor |
| Chronic Kidney Disease | Relative rate (adjusted)[54] | 1.4 | [1.3-1.5] | Risk Factor |

Table 3 summarises PAD risk factors with their pooled, matched or adjusted odds ratios.

Table 3: PAD risk factors with their pooled, matched or adjusted odds ratios

| Risk Factor | Type of Odds Ratio | Odds Ratio | 95% CI | Effect on Outcome |
| --- | --- | --- | --- | --- |
| Age | OR (pooled)[7] |  |  |  |
| Per 10 year increase |  | 1.39 | [1.34-1.44] | Risk Factor |
| Gender | OR (pooled)[7] |  |  |  |
| Female |  | 1.00 |  | Reference |
| Male (overall) |  | 0.83 | [0.74-0.93] | Protective |
| Male (HIC) |  | 1.43 | [1.18-1.73] | Risk Factor |
| Male (LMIC) |  | 0.50 | [0.43-0.57] | Protective |
| Ethnicity | OR (adjusted)[32] |  |  |  |
| Non-Hispanic white |  | 1.00 |  | Reference |
| Non-Hispanic black |  | 2.39 | [1.11-5.12] | Risk Factor |
| Mexican American |  | 1.15 | [0.59-2.24] | NS |
| Other |  | 0.57 | [0.07-4.56] | NS |
| Hypertension | OR (pooled) |  |  |  |
| Normotensive |  | 1.00 |  | Reference |
| BP ≥ 140/90 mm Hg |  | 1.47 | [1.37-1.57] | Risk Factor |
| Diabetes | OR (pooled) )[7] |  |  |  |
| No diabetes |  | 1.00 |  | Reference |
| FPG > 7mmol/L, on medication, doctor diagnosis |  | 1.68 | [1.53-1.84] | Risk Factor |
| Smoking | OR (pooled) )[7] |  |  |  |
| Never smokers |  | 1.00 |  | Reference |
| Current smokers |  | 2.09 | [1.91-2.09] | Risk Factor |
| Former smokers |  | 1.87 | [1.64-2.18] | Risk Factor |
| Obesity | OR (pooled) )[7] |  |  |  |
| BMI ≤ 25 kg/m2 |  | 1.00 |  | Reference |
| BMI > 25 kg/m2 |  | 0.83 | [0.75-0.91] | Protective |
| Dyslipidaemia | OR (pooled) )[7] |  |  |  |
| Hypercholesterolaemia |  | 1.16 | [1.08-1.25] | Risk Factor |
| Hypertriglyceridaemia |  | 1.22 | [1.10-1.35] | Risk Factor |
| Elevated LDL |  | 1.03 | [0.94-1.13] | NS |
| Low HDL |  | 0.82 | [0.83-1.01] | NS |
| Inflammatory markers | OR (pooled) )[7] |  |  |  |
| CRP > 2.9 mg/dL |  | 1.69 | [1.13-2.54] | Risk Factor |
| Hyperviscosity/ Hypercoagulable state | OR (pooled) )[7] |  |  |  |
| Fibrinogen >400 mg/dL |  | 1.07 | [1.00-1.14] | NS |
| Personal History of CVD | OR (pooled) )[7] |  |  |  |
| CVD history |  | 2.27 | [1.98-2.59] | Risk Factor |
| Chronic Kidney Disease |  |  |  |  |
| ABI 1.0-1.3 | OR (adjusted) [58] | 1.0 |  | Reference |
| ABI >1.3 |  | 1.0 | [0.4-2.7] | NS |
| ABI 0.9-1.0 |  | 1.2 | [0.5-2.8] | NS |
| ABI < 0.9 |  | 2.5 | [1.2-5.1] | Risk Factor |
| eGFR <60 | OR (adjusted) [6] | 2.0 | [1.4-2.7] | Risk Factor |
| Atrial Fibrillation | HR (adjusted)[59] |  |  |  |
| No AFib + No comorbidity |  | 1.00 |  | Reference |
| AFib + No Comorbidity |  | 2.29 | [1.17-4.49] | Risk Factor |
| AFib + Comorbidity |  | 3.89 | [2.82-5.36] | Risk Factor |
| Family History | OR (adjusted) |  |  |  |
| Overall |  | 1.97 | [1.60-2.42] | Risk Factor |
| Parental |  | 2.30 | [1.56-3.39] | Risk Factor |
| Sibling |  | 1.86 | [1.46-2.38] | Risk Factor |

## PAD prevalence from the literature

Table 4 shows prevalence estimates of PAD in the USA using National Health and Nutrition Examination Survey (NHANES) in the civilian, non-institutionalized population over the period 1999–2004. [6]

Table 4: prevalence estimates of PAD from Eraso et al. [6]

| *n =*7058 | Prevalence of PAD % (SE) | *p*-value |
| --- | --- | --- |
| Overall | 4.64 (0.29) |  |
| Age groups |  | <0.01 |
| 40–49 | 1.43 (0.29) |  |
| 50–59 | 3.41 (0.58) |  |
| 60–69 | 7.77 (0.77) |  |
| 70 & over | 16.62 (1.09) |  |
| Gender |  | <0.01 |
| Male | 3.54 (0.38) |  |
| Female | 5.57 (0.46) |  |
| Race/ethnicity |  | <0.01 |
| Non–Hispanic White | 4.66 (0.32) |  |
| Non-Hispanic Black | 7.46 (0.79) |  |
| Mexican-American | 3.11 (0.62) |  |
| Other | 2.06 (0.53) |  |
| BMI | 0.20 |  |
| <25 | 4.63 (0.55) |  |
| 25–30 | 4.09 (0.35) |  |
| >30 | 5.29 (0.58) |  |
| Smoking |  | <0.01 |
| Never | 3.73 (0.40) |  |
| Current | 5.44 (0.49) |  |
| Former | 5.46 (0.55) |  |
| Diabetes |  | <0.01 |
| Yes | 9.57 (1.31) |  |
| No | 4.00 (0.28) |  |
| Hypertension |  | <0.01 |
| Yes | 7.61 (0.63) |  |
| No | 2.33 (0.26) |  |
| Kidney function |  | <0.01 |
| eGFR >90 | 2.99 (0.41) |  |
| eGFR 60–90 | 3.77 (0.29) |  |
| eGFR <60 | 15.33 (1.81) |  |
| Hypercholesterolemia |  | <0.01 |
| Yes | 5.56 (0.41) |  |
| No | 3.73 (0.34) |  |

Table 5 shows PAD prevalence among high-risk groups based on gender and race/ethnicity stratum, again from Eraso et al’s NHANES analysis.[6]

Table 5: PAD prevalence among high-risk groups based on gender and race/ethnicity stratum[6]

|  |  |  | Non-Hispanic White |  | Non-Hispanic Black |  | Mexican American |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Gender | Race/ethnicity | *n* | PAD, % (S.E) | *n* | PAD, % (SE) | *n* | PAD, % (SE) |
| Males | Age >70 years | 671 | 15.13 (1.46) | 109 | 19.43 (3.26) | 154 | 20.85 (3.78) |
|  | Diabetes | 302 | 10.97 (2.15) | 146 | 18.75 (2.77) | 189 | 6.40 (1.83) |
|  | Current Smoker | 382 | 7.15 (1.04) | 198 | 10.77 (2.44) | 180 | 2.76 (0.90) |
|  | CKD | 345 | 14.85 (2.28) | 61 | 18.57 (5.55) | 46 | 10.27 (4.10) |
|  | Hypertension | 1037 | 7.94 (0.84) | 378 | 9.26 (1.23) | 354 | 7.33 (2.02) |
|  | Hypercholesterolemia | 1073 | 5.69 (0.72) | 260 | 9.85 (1.75) | 368 | 3.39 (1.03) |
| Females | Age >70 years | 603 | 16.81 (1.61) | 109 | 25.33 (4.43) | 134 | 19.97 (3.08) |
|  | Diabetes | 208 | 12.89 (2.73) | 136 | 12.77 (2.65) | 170 | 7.43 (1.93) |
|  | Current Smoker | 312 | 7.02 (1.25) | 122 | 8.91 (2.46) | 90 | 2.43 (1.23) |
|  | CKD | 389 | 16.63 (2.44) | 66 | 21.74 (4.61) | 64 | 18.84 (4.05) |
|  | Hypertension | 1027 | 9.68 (1.03) | 420 | 12.01 (1.71) | 385 | 6.84 (1.18) |
|  | Hypercholesterolemia | 1016 | 8.06 (0.82) | 298 | 10.20 (2.02) | 380 | 6.52 (1.34) |

Table 6 shows the odds ratios of PAD, again from NHANES 1999–2002.

Table 6: odds of PAD, NHANES 1999–2002[6]

|  |  |  |  |
| --- | --- | --- | --- |
|  | Odds Ratios | 95% CIs | P values |
| Diabetes | 1.5 | 1.0-2.3 | 0.04 |
| Hypertension | 1.5 | 0.9-2.2 | 0.05 |
| Current smoker | 4.1 | 3.1-5.4 | <0.01 |
| Former smoker | 1.8 | 1.3-2.5 | <0.01 |
| Chronic kidney disease (eGFR < 60) | 2.0 | 1.4-2.7 | <0.01 |
| Hypercholesterolemia | 1.3 | 1.0-1.8 | 0.03 |
| Obesity (BMI > 30) | 1.0 | 0.7-1.4 | 0.58 |

Table 7 shows the prevalence of PAD by age and sex in differing groups of countries from Fowkes et al in 2013.[7]

Table 7: prevalence of PAD by age and sex from Fowkes et al. (2013)[7]

|  | Female | | Male | |
| --- | --- | --- | --- | --- |
| Age Group | High Income Countries (%) | Low-Middle Income Countries (%) | High Income Countries (%) | Low-Middle Income Countries (%) |
| 25-29 years | 2.70 | 3.96 | 2.76 | 1.21 |
| 30-34 years | 3.20 | 4.46 | 3.27 | 1.50 |
| 35-39 years | 3.78 | 5.01 | 3.88 | 1.87 |
| 40-44 years | 4.47 | 5.62 | 4.58 | 2.33 |
| 45-49 years | 5.28 | 6.31 | 5.41 | 2.89 |
| 50-54 years | 6.23 | 7.08 | 6.38 | 3.58 |
| 55-59 years | 7.33 | 7.92 | 7.51 | 4.43 |
| 60-64 years | 8.60 | 8.87 | 8.82 | 5.47 |
| 65-69 years | 10.08 | 9.91 | 10.33 | 6.74 |
| 70-74 years | 11.77 | 11.05 | 12.07 | 8.28 |
| 75-79 years | 13.71 | 12.32 | 14.05 | 10.13 |
| 80-84 years | 15.91 | 13.70 | 16.30 | 12.33 |
| 85-89 years | 18.38 | 15.22 | 18.83 | 14.94 |
| 90-94 years | 21.14 | 16.87 | 21.65 | 17.99 |
| 95-99 years | 24.20 | 18.65 | 24.77 | 21.50 |

# Methods

## “Data discovery” from UK survey data sources

We considered four potential data sources from different health surveys conducted in the UK. Using these we conducted a data discovery procedure, comparing each source for their coverage of risk factor and outcome variables for CVD. The results are summarised in Table 5.

### Whitehall II

The Whitehall II study is a prospective cohort study of individuals employed by the British Civil Service at the time of recruitment, between 1985 and 1988.[60] This study follows from the first Whitehall study initiated 1967, with the broad aim of determining disparities in health equality as they relate to socioeconomic factors. The first phase recruited 10,308 individuals (3414 women and 6985 men) between the ages of 35 and 55 years. The cohort is invited to clinical research screenings at 5-year intervals with postal questionnaires sent to participant between clinical screenings. Telephone questionnaires are administered to those unwilling or unable to attend the clinic or complete the full postal questionnaire, and as of phase 7 home nurse visits were offered to those unable or unwilling to attend the clinic. To date there are nine waves of data collection available.

Questionnaires cover a broad range of health, socioeconomic, and demographic information, including self-reported disease diagnosis, medication, as well as food frequency questions. Clinical measures include a wide range of biomarkers from blood samples, anthropometric measurements, and blood pressure. Participants are also administered an electrocardiogram. Clinical records for cardiovascular events self-reported on the questionnaire or determined by ECG are verified through hospital and primary care records. Mortality is followed through the NHS Central Registry, providing date and cause of death for Whitehall study participants.

### AIRWAVE Health Monitoring Study

The AIRWAVE Health Monitoring Study is a prospective cohort study commissioned in 2003 for the original purpose of assessing the long-term health effects of the Terrestrial Trunked Radio (TETRA) communication system among British police officers. It has subsequently been expanded to look at the general health of the police force in Britain. Participation is open to all 54 police forces in Great Britain, and all police staff are eligible to enrol. Since the initial pilot studies began in 2004, 28 forces have since been enrolled. The organisers aim to recruit a total of 60,000 participants in total. As of December 2012, there were 42,897 individuals in the database, of which 42,112 have been linked to National Health Service (NHS) records.

Data collection for the AIRWAVE study is divided into two phases. The first phase consists of a questionnaire to be completed upon enrolment in the study. Questions cover demographic, health and lifestyle information. The second phase involves a second, more in depth questionnaire as well as a health screening. Nurses performed clinical examination of participants, collecting measurements of blood pressure, arterial stiffness, weight, height, waist and hip circumference and body composition as well as administering and electrocardiogram (ECG). Systolic and diastolic blood pressure (SBP and DBP) were also measured. Blood samples are collected, providing biomarkers including lipid profiles, inflammatory markers, and measures of glucose tolerance.

### Health Survey for England 2013

Health Survey for England (HSfE) is an annual cross-sectional survey carried out in England since 1991, designed to assess changes in health outcomes and lifestyle among the British population. The survey design incorporates both children and adults, representative of the general population at a national and regional level. Households and individuals are randomly selected. The 2013 survey included 8795 adults (aged 16 years and over) and 2185 children (age 0-15 years), of which 6183 adults and 1455 children also received a nurse visit for clinical measurements. These included anthropometric and blood pressure measurements as well as blood samples for various biomarkers. The survey questionnaire relies largely on self-reported diagnosis of medical conditions as well as various risk factors.

### English Longitudinal Study of Ageing

The English Longitudinal Study of Ageing (ELSA) is a prospective cohort study designed to assess the health and well-being of the English population over the age of 50. Study participants for the initial wave were drawn from HSfE who were over the age of 50 at the time of recruitment, and included 12,099 individuals aged 50 to 100 years. The study population was refreshed during the third wave of data collection to replenish the sample in the younger age range. Participants complete a face-to-face interview and self-completion questionnaire every two years, and are assessed by a nurse every four years. To date, seven waves of data are available. Questionnaires cover a broad range of characteristics related to physical and mental health, economics and general well-being. The nurse assessment includes clinical measurements of anthropometry, blood pressure, lung function, as well as taking a blood sample which provides data on various biomarkers of disease.

Table 8 shows coverage of risk factor variables from the potential data sources we examined.

Table 8: coverage of risk factor variables from potential data sources

| Risk Factor | Whitehall II | AIRWAVE | HSfE 2013 | ELSA |
| --- | --- | --- | --- | --- |
| Age | Yes – May need to be derived | Yes | Yes – age and age band | Yes |
| Gender | Yes | Yes | Yes | Yes |
| Ethnicity | Yes- Only white/non-white | Text variable from questionnaire | Yes – 18 categories | Yes – Only white/non-white |
| Smoking | Yes/No; cigarettes/day; current/former | Yes/No; cigarettes/day; current/former | Yes/No; cigarettes/day; current/former; cotinine as biomarker | Yes/No; cigarettes/day; current/former |
| Diabetes | Self-reported diagnosis; HbA1c, HOMA-IR, FPG clinical measurements; family history; medication | Self-reported diagnosis – type 1 vs. type 2; HbA1c, FPG and C-peptide clinical measurements | Self-reported diagnosis – type 1 and type 2; HbA1c clinical measure; medications | Self-reported diagnosis; HbA1c and FPG clinical measures; medication |
| Hypertension | Self-reported diagnosis and treatment; SBP and DBP clinical measures; family history | Self-reported diagnosis; clinical SBP and DBP measures; diet questionnaire | Self-reported diagnosis; SBP, DBP and MAP clinical measures; comprehensive medication questions | Self-reported diagnosis; SBP, DBP and MAP clinical measures; self-reported medications |
| Dyslipidaemia | Clinical measures for Total, HDL, IDL, LDL, Apolipoproteins A and B, and triglycerides; diet questionnaire | Self-reported diagnosis; diet questionnaire; Total cholesterol, HDL, Apolipoproteins A and B clinical measures (No triglycerides) | Total cholesterol and HDL clinical measure; high vs. low TC and HDL from clinical; medication | Clinical measures for Total, HDL, LDL, and triglycerides |
| Obesity | BMI, fat mass, fat percentage, waist circumference and WHR clinical measures | Body fat %, impedance waist circumference, WHR, BMI clinical measures | Self-reported; BMI, WHR, WC clinical measures (pre-grouped) | BMI, waist circumference and WHR clinical measures |
| Family History | Angina/MI and stroke questionnaire for parents/siblings; nothing for PAD | Asks if parents died from MI or stroke (no non-fatal, sibling or anything on PAD) | NO VIABLE VARIABLES | Cause of death of parents |
| Physical Activity | METs; breakdown by activity based on self-reports | Self-reported frequency of activity/inactivity | Self-reported time spent (pre-grouped) | Self-reported frequency |
| Alcohol Consumption | Self-reported Yes/No, units per week | Self-reported Yes/No, frequency, units | Self-reported Yes/No, frequency, units | Maximum consumed; Yes/No |
| Inflammatory Markers | CRP and IL-6 clinical measures | CRP clinical measure | NO VIABLE VARIABLES | CRP clinical measure |
| Hyper-viscosity/hyper-coagulable state | Factor VII, Fibrinogen, plasma viscosity, von Willebrand’s factor clinical measures | Fibrinogen, prothrombin time, haematocrit | Self-reported clotting disorder; self-reported anti-platelet medication | Hemoglobin and fibrinogen clinical measures; self-reported clotting disorder |
| Hyperchromocysteinaemia | NO VIABLE VARIABLES | NO VIABLE VARIABLES | NO VIABLE VARIABLES | NO VIABLE VARIABLES |
| Chronic Renal Insufficiency | Diet questionnaire; clinical EGFR measurements | Creatinine clinical measure; Diet questionnaire | NO VIABLE VARIABLES | Self-reported kidney trouble |
| Socioeconomic Status | IMD 2004 and 2007; Townsend Index |  | IMD score |  |

Table 9 shows coverage of outcome variables from the potential data sources we examined.

Table 9: coverage of outcome variables from potential data sources

| Outcome | Whitehall II | AIRWAVE | HSfE 2013 | ELSA |
| --- | --- | --- | --- | --- |
| Coronary Heart Disease | Self-reported angina; Self-reported CABG operation; Self-reported heart disease risk; Self-reported hospital admission; Self-reported ischemia; Self-reported nitrates; ECG (results and Minnesota codes)  Clinical records of hospitalisation  Self-reported angiogram/angioplasty??  Self-reported chest pain??  Self-reported other heart troubles??  Clinical heart rate variability measures?? | Self-reported diagnosis of angina/MI  Self-reported CABG operation  Clinical ECG interpretation  ECG (results and Minnesota codes)  Self-reported chest pain??  Self-reported other heart tests/operation??  Self-reported angiogram/angioplasty?? | Self-reported MI/angina diagnosis (longstanding illness)  Self-reported heart/circulatory disease (non-specific)??  Self-reported medication | Self-reported angina |
| Cerebrovascular Disease | Self-reported doctor diagnosis  Self-reported slurred speech, visual symptoms, weakness | Self-reported stroke /TIA diagnosis | Self-reported stroke (longstanding illness) | Self-reported stroke |
| Peripheral Arterial Disease | Self-reported diagnosis of IC  Self-reported leg pain  Self-reported angiogram/angioplasty?? | NO VIABLE OUTCOME MEASURES | NO VIABLE OUTCOME MEASURES | Self-reported IC diagnosis  Self-reported leg pain whilst walking |

While all of the surveys contained variables for most of the risk factors, only Whitehall II and ELSA had means of assessing PAD as an outcome. Ultimately, it was decided to use Whitehall II as the data source for our model, as the PAD-related questions allowed us to more definitively classify individuals with this disease. Furthermore, Whitehall II has a wider range of variables for specific CVD risk factors, particularly with the clinical records and wider range of biomarker data.

## Definition of Outcomes

### PAD

As with CHD and stroke, we developed a diagnostic algorithm for PAD based on a literature review and expert advice, shown in Figure 3. Unfortunately there is no clinical measurement of Ankle Brachial Pressure Index (ABPI) in Whitehall II, which is the standard criterion for PAD diagnosis. Thus the variables to assess PAD come from the questionnaire, which asks patients to report any diagnosis of intermittent claudication as well as asking a series of questions regarding leg pain while walking (Table 10). After exploratory analysis, it was shown that a very high proportion of the participants responded positively to the questions on leg pain. It is likely that this may have been interpreted broadly by the participants (e.g. individuals with arthritis or muscle cramps may have been included). We therefore divided PAD into two categories for analysis: 1) definite PAD cases which included only the variables ticlau and jinclau (self-reported doctor-diagnosed intermittent claudication); and 2) potential PAD cases which included all individuals responding positively to any of the questions on leg pain

Table 10: Variables in Whitehall II related to PAD

|  |  |
| --- | --- |
| Variable Name | Variable Description |
| ticlau, jinclau | Intermittent claudication/bad circulation in arteries – ever told |
| lpcalf | Leg pain in calves |
| lplev | Leg pain when walking on the flat |
| lpuph | Leg pain when walking uphill |
| legpain | Leg pain whilst walking |
| lpstill | Leg pain begins when standing/sitting i.e. probably not PAD |
| lpstopgo | Leg pain disappears when walking i.e. probably not PAD |

## Risk factor variables

We used the literature review described in the Background to extract data on risk factors. There were two main reasons why some risk factors from the literature were not used in the final model. Firstly, the data was not available in Whitehall II. For example, there was no means of assessing hyperhomocysteinaemia based on the data collected. However for most of the established risk factors we were able to identify appropriate variables.

Secondly, to produce local estimates we use “joint distributions” (i.e. cross tabulations which distribute data on each risk factor across the data for all other risk factors) of local risk factor data to which we apply the Whitehall II prevalence estimates for the same distributions. Hence we can only use in the final regression model variables which are also available locally. This may cause model performance to deteriorate. We evaluated the extent of this by comparing Receiver Operating Characteristic (ROC) curves for the two models.

### Age

All participants provided their year of birth at baseline. We used this variable, ‘yob\_c’, to calculate the age of each participant as of the most recent phase of data collection in 2009. We then used this to generate the variable ‘**age\_gp**’, grouping individuals into age categories in 5 year bands: 55-59 years, 60-64 years, 65-69 years, 70-74 years, and 75-79 years.

### Sex

The variable ‘**sex**’ was used to classify individuals as male or female.

### Ethnicity

Whitehall II only classifies individuals’ ethnicity as either white or non-white. This is coded in the variable ‘ethn\_ds’, which was relabelled as **‘ethnicity**’.

### Hypertension

There are several possible ways of classifying individuals with hypertension in Whitehall II. Data collected from questionnaires contains information on self-reported doctor-diagnosed hypertension. In addition there is a derived variable for anti-hypertensive medication, based on self-reported prescribed medication. However, in order to prevent biased estimates from inaccurate self-reports, we chose to use the clinical measurements of systolic and diastolic blood pressure, which may identify undiagnosed cases of hypertension. We combined each of these to create the binary variable ‘hypertension’ for use in regression analysis. Table X shows the variables related to hypertension.

* ‘hypertension’ coded as 1 (Hypertension) if any of the following criteria were met:
* Participant responded positively to question of hypertension diagnosis during any phase of data collection
* Participant responded positively to being prescribed an anti-hypertensive drug during any phase of data collection
* Systolic blood pressure reading was greater than 140 mmHg during any phase of data collection
* Diastolic blood pressure reading was greater than 90 mmHg during any phase of data collection
* ‘hypertension’ coded as 0 (No hypertension) if none of the above criteria were met

Table 11: Whitehall II variables related to hypertension

| Variable Label | Phase 1 | Phase 2 | Phase 3 | Phase 4 | Phase 5 | Phase 6 |  | Phase 8 | Phase 9 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| High blood pressure – Ever told | bpup | zbpup |  | vhbp | thbp |  |  |  |  |
| Drug subclass – antihypertensives | antihyp | zantihyp | xantihyp | vantihyp | tantihyp | qantihyp |  | mantihyp |  |
|  |  |  |  |  |  |  |  |  |  |

### Dyslipidaemia

Whitehall II does not contain any questions for self-reported diagnosed dyslipidaemia. There is however a derived variable classifying self-reported medication into lipid lowering drugs as well as statins specifically. In addition, blood tests for total cholesterol, HDL and LDL cholesterol, and triglycerides are available from clinical assessments in phases 1, 3, 5, 7 and 9. We combined these variables to generate the binary variable ‘**dyslipidaemia’** as follows:

* ‘dyslipidaemia’ coded as 1 (Dyslipidaemia) if any of the following criteria met:

1. Participant responded positively to being prescribed a lipid-lowering drug or statin during any phase of data collection
2. Blood cholesterol ≥6.2 mmol/L in any phase of data collection
3. HDL cholesterol ≤ 1 mmol/L in any phase of data collection
4. LDL cholesterol ≥ 4.1 mmol/L in any phase of data collection
5. Triglycerides ≥ 1.7 mmol/L in any phase of data collection

* ‘dyslipidaemia’ coded as 0 (No dyslipidaemia) if none of the above criteria were met

Table 12: Whitehall II variables related to dyslipidaemia

| Variable Label | Phase 1 | Phase 3 | Phase 4 | Phase 5 | Phase 6 | Phase 7 | Phase 8 | Phase 9 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug subclass: lipid lowering | drug3 |  | vlipdrg | tlipdrg | qlipdrg | mlipdrg | klipdrg | jlipdrg |
| Drug subclass: statins |  |  |  |  |  |  | kstatins |  |
| Blood cholesterol | blchol | xblchol |  | tblchol |  | mblchol |  | jblchol |
| High density lipoprotein | hdl | xhdl |  | thdl |  | mhdl |  | jhdl |
| Low Density Lipoprotein, mm |  | xldl |  | tldl |  | mldl |  | jldl |
| Triglyceride | trig | xtrig |  | ttrig |  | mtrig |  | jtrig |

### Family History (CHD)

Whitehall II variables related to family history of coronary heart disease come from questionnaire data, based on questions about whether parents or siblings have suffered from heart attack or angina. In addition, questions regarding parents’ cause of death contains an option for heart attacks.

Table 13: Whitehall II variables related to family history

|  |  |  |  |
| --- | --- | --- | --- |
| Variable Label | Phase 1 | Phase 2 | Phase 7 |
| Father: cause of fathers death (=1 for heart attack) | codf | zcodf | mcodf |
| Mother: mothers cause of death (=1 for heart attack) | codm | zcodm | mcodm |
| Angina – Either parent suffered angina | angpar |  |  |
| MI – either parent suffered a heart attack | hapar |  |  |
| MI – any sibling suffered a heart attack | hasib | zhasib |  |

We generated the variable **‘famhx\_chd’** to indicate a whether a participant had a family history of heart disease:

* ‘famhx\_chd’ coded as 1 (Family history) if either parent or sibling suffered from heart attack or angina OR if either parent reported as having died from a heart attack in any phase of data collection
* ‘famhx\_chd’ coded as 0 (No family history) if no parent or sibling suffered heart attack or angina AND neither parent reported as having died from heart attack

### Family History (Stroke)

Similar to family history of heart disease, the variables for family history of stroke stem from self-reports in the questionnaires on whether either parent or any sibling has suffered a stroke. The parents’ cause of death variable also has an option for stroke.

| Variable Label | Phase 1 | Phase 2 | Phase 7 |
| --- | --- | --- | --- |
| Father: cause of fathers death (=2 for stroke) | codf | zcodf | mcodf |
| Mother: mothers cause of death (=2 for stroke) | codm | zcodm | mcodm |
| Stroke – Either parent suffered a stroke | strpar |  |  |
| Stroke – Any sibling suffered a stroke | strsib | zstrsib |  |

We generated the variable **‘famhx\_str’** to indicate whether a participant had a family history of stroke:

* ‘famhx\_str’ coded as 1 (Family history) if either parent or any sibling suffered from stroke OR if either parent died from a stroke in any phase of data collection
* ‘famhx\_str’ coded as 0 (No family history) if no parent or sibling suffered stroke AND neither parent died from a stroke

### Smoking

There are a number of variables related to smoking status in Whitehall II, with questions on the number and type of tobacco smoked. We used the derived variable labelled ‘Smoking habits (never/ex/current)’ to classify each participant’s smoking status for our analysis. As with other variables we used the most recent wave for which information was available on each participant, as smoking habits may change over time. Information was available is phases 1, 2, 3, 5, 7, and 9. We generated the variable ‘**smoke\_cat’** as follows:

* ‘smoke\_cat’ coded as 1 (Never Smoker) if participant classified as ‘never-smoker’ during most recent phase for which data is available for that individual
* ‘smoke\_cat’ coded as 2 (Former Smoker) if participant classified as ‘ex-smoker’ during most recent phase for which data is available for that individual
* ‘smoke\_cat’ coded as 3 (Current Smoker) if participant classified as ‘current smoker’ during most recent phase for which data is available for that individual

Table 14: Whitehall II variables related to smoking

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Variable Label | Phase 1 | Phase 2 | Phase 3 | Phase 5 | Phase 7 | Phase 9 | | Smoking habits (never/ex/current) | esmoke | zesomke | xesmoke | tesmoke | mesmoke | jesmoke | |

### Obesity

There are several different ways of measuring obesity based on the clinical assessment. These include BMI, fat percentage, waist circumference and waist-hip ratio. We chose to use BMI as this is the most commonly used measurement of obesity in epidemiological studies on CVD. Using the variable labelled ‘Body mass index’ we categorised participants into five categories based on WHO classification guidelines (ref). Once again, we used the most recent phase for which data was available for each individual. We generated the variable ‘**bmi\_cat’** as follows:

* ‘bmi\_cat’ coded as 1 (Underweight) if BMI <18.5 kg/m2 during most recent phase for which data is available for that individual
* ‘bmi\_cat’ coded as 2 (Normal Weight) if BMI ≥18.5 kg/m2 and ≤25 kg/m2 during most recent phase for which data is available for that individual
* ‘bmi\_cat’ coded as 3 (Overweight) if BMI >25 kg/m2 and ≤30 kg/m2 during most recent phase for which data is available for that individual
* ‘bmi\_cat’ coded as 4 (Obese) if BMI >30 kg/m2 and ≤35 kg/m2 during most recent phase for which data is available for that individual
* ‘bmi\_cat’ coded as 5 (Severely Obese) if BMI >35 during most recent phase for which data is available for that individual

Table 15: Whitehall II variables related to obesity

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable Label | Phase 1 | Phase 3 | Phase 5 | Phase 7 | Phase 9 |
| Body mass index | bmi | xbmi | tbmi | mbmi | jbmi |

### Diabetes

There are several potential ways to ascertain whether an individual has diabetes in Whitehall II. In addition to self-reports from questionnaires there are clinical measures of HbA1c, fasting plasma glucose and HOMA-IR. We decided to use the derived variable ‘jdmincum’, which tabulates the total number of diabetes cases in the cohort. The variables ‘jdmincum’ was relabelled ‘**diabetes**’ and used for regression analysis.

### Chronic Kidney Disease

Chronic kidney disease is clinically diagnosed based on EGFR value ≤60 mL/min/1.73m2 (ref). EGFR was first assessed during clinical examination in Whitehall II only in the most recent phase (Phase 9). As such there is a substantial amount of missing data for this risk factor (n=4242, 41% missing). We used the variable ‘jegfr’ to create the binary variable ‘**ckd**’ as follows:

* ‘ckd’ coded as 1 (Chronic kidney disease) if jegfr ≤60 mL/min/1.73m2
* ‘ckd’ coded as 0 (No chronic kidney disease) if jegfr >60 mL/min/1.73m2

### “Hypercoagulable state”/on anti-coagulant

Clinical biomarkers for a number of different clotting factors are available in Whitehall II (Table X). However we were unable to find consensus criteria on the use of these in the clinical diagnosis of a hypercoagulable state. We therefore had to rely on self-reports of anti-coagulant medication use to identify individuals in a hypercoagulable state. This method may not be ideal, as individuals who have had heart attacks and stroke are often prescribed anti-coagulant medication as a treatment, creating a question of the direction of causality. We generated the variable ‘**hypercoagulation**’ based on self-reported medication use only. However due to the potential for confounding by reverse causality, we constructed models both including and excluding this variable:

* ‘hypercoagulation’ coded as 1 (Hypercoagulation) if participant reported being prescribed anti-coagulant or anti-platelet drugs during any phase of data collection. There was insufficient time for anticoagulants and antiplatelet agents to have been considered separately
* ‘hypercoagulation’ coded as 0 (No hypercoagulation) if participant never reported use of anti-coagulant or anti-platelet drugs

Table 16: Whitehall II variables related to hypercoagulation

| Variable Label | Phase 1 | Phase 3 | Phase 4 | Phase 5 | Phase 6 | Phase 7 | Phase 8 | Phase 9 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug subclass: Anticoagulant drugs | drug4 |  |  |  |  |  |  |  |
| Drug subclass: Antiplatelets |  |  | vdrg29 | tdrg29 | qdrg29 | mdrg29 | kdrg29 | jdrg29 |
| Factor VII | fact7 | xfactor7 |  |  |  |  |  |  |
| Fibrinogen | fib | xfibrin |  | tfibrin |  |  |  |  |
| Plasma viscosity (plasma) |  |  |  | tplasvis |  |  |  |  |
| Von Willebrand’s factor |  | xvwf |  |  |  |  |  |  |

### Inflammatory Markers

Clinical biomarkers for CRP and IL-6 are available in Whitehall II. We restricted our analysis to CRP as this has a more defined cut-off for defining normal levels. Blood tests for CRP were performed in phases 3, 5 and 7, with at least one measurement available for 8467 (82%) individuals. We used a value of CRP≥3 g/L to define high levels of CRP. The variable **‘high\_crp**’ was generated as follows:

* ‘high\_crp’ coded as 1 (High CRP) if CRP ≥3 g/L in any phase of data collection
* ‘high\_crp’ coded as 0 (Normal CRP) if CRP < 3 g/L for all phases of data collection

However as we had no immediately available local data on anti-coagulant use we have not considered this variable further. We do have a database of practice-level prescribing data but there was insufficient time to use it.

### Socioeconomic status/deprivation

Whitehall II contains several indices of deprivation, including the Indices of Multiple Deprivation 2004 and 2007 (IMD 2004 and 2007) as well as the Townsend Index. While the Townsend Index has fewer missing values in the dataset, we chose IMD 2007 as this is more commonly used. Participants were categorised into quintiles based on their IMD 2007 score, and the variable **‘ses’** was created containing this information.

### Physical Activity

We intended to include physical activity in the modelling but abandoned this because the categories used in Whitehall II are too different from those in the local physical activity data provided by the Sport England *Active People* survey.

## Statistical Analyses

### Whitehall II missing data

When performing logistic regression with multiple variables, Stata performs list-wise deletion by default, so that any individual missing a value for any of the outcome or risk factor variables is excluded from the analysis. This can result in potential biases and a loss of statistical power to assess associations. While most of the risk factors have no or very few missing values, there are several with very poor coverage in the dataset e.g. many participants are missing an IMD score. In order to deal with this, we used multiple imputation to impute all missing values for risk factors.

### Whitehall II descriptive analyses

We performed a number of descriptive analyses on the patient-level dataset including demographics, risk factor breakdowns and categories.

### Whitehall II regression modelling

We fitted univariate then multivariate logistic regression models as described in previous publications, to produce odds ratios (ORs) and regression coefficients.[61] A range of multivariate regression models were fitted in order to obtain the best performing. We included one additional variable at a time to observe the effects. We performed backwards and forwards stepwise variable selection in the multivariable models. Stata has a *stepwise* command which automates this procedure but we perfomed variable selection manually using likelihood ratios and Wald tests because we had used multiple imputation of missing data.

Deprivation has been shown to be a risk factor for CVD. For example, QRISK2, the individual CVD predictive risk score recommended by NICE, found that deprivation (in the form of Townsend scores) and ethnicity were separate risk factors.[33] The variables included in the final model are also determined by the availability of local data to match with the model variables. Hence variable selection has to be a compromise between the best model which can be produced from Whitehall II data and the local variable available.

We have over time increased the number of variables used in the local models as more local data has become available. However as more variables are added we need to take account of the joint effects of multiple risk factors, i.e. it assumes they operate independently. Estimation of the joint effects of multiple risk factors is complex for several reasons. In particular, some of the effects of more distal risk factors are mediated through intermediate factors.

Finally, there can be collinearity between exposure to various risk factors, meaning that one can be linearly predicted from the others with a substantial degree of accuracy. In this situation the coefficient estimates of the multiple regression may change erratically in response to small changes in the model or the data. Collinearity does not reduce the predictive power or reliability of the model as a whole, at least within the sample data set; it only affects calculations regarding individual predictors. That is, a multiple regression model with correlated predictors can indicate how well the entire bundle of predictors predicts the outcome variable, but it may not give valid results about any individual predictor, or about which predictors are redundant with respect to others.

### Interactions

There is an interaction between the effects of two exposures if the effect of one exposure varies according to the level of the other exposure.[62] For example, there might be an interaction between the back pain risk factors of education level and social class. An alternative term for interaction is effect modification. In this example, we can think of this as educational level modifying the effect of social class. The most flexible approach to examine interactions is to use regression models, but when using Mantel-Haenszel methods to control for confounding an alternative is to use a χ2 test for effect modification, commonly called a test of heterogeneity. Interaction, effect modification and heterogeneity are three different ways of describing the same thing. Log likelihoods are compared in the two models excluding and including the interaction parameters to test the null hypothesis that there is no interaction between selected variables.

### Internal validation

We fitted a range of multivariate logistic regression models in order to obtain the best performing. We included one additional variable at a time to observe the effects. In order to obtain the most parsimonious models we then applied stepwise backward and forward variable selection using the *stepwise* command in Stata. Finally, we internally validated the models by generating receiver operating characteristic (ROC) curves, by using the ***predict*** regression post-estimation command to generate for each respondent the probability of having PAD using the derived odds ratios (ORs), and by using these probabilities to examine sensitivity and specificity.

All statistical analysis was carried out in Stata SE14 or MP14.

## Local prevalence estimates

Derived ORs (or rather, regression coefficients) are used to estimate prevalence in small population subgroups. Local population breakdowns for each risk factor are used, where these are available. ICL has a wide range of small population risk factor prevalence breakdowns, including age, sex, deprivation, smoking, ethnicity, cardiovascular diseases and other disease conditions. The local model uses locally available data.

The “local” model includes only those variables that are available at local population level i.e. age, sex, socioeconomic status, BMI, smoking status, depression and other disease conditions. The steps in applying the prevalence estimates are as follows and in the equations below:

• Use the regression coefficients to generate log odds (since they are from a logistic regression model) for each risk factor subcategory

• Generate a similar table of odds by exponentiation

• Generate a similar table of prevalence in each risk factor subcategory using the epidemiologic formula

• Produce a matching table of small population subcategories. If there are no corresponding local data with a sufficiently granular breakdown e.g. ethnicity by age by sex, this requires deciding how each risk factor should be attributed across other risk factor categories, with evenly as the default. For example, we used the national age/sex/ethnicity breakdown from the Census and age/smoking breakdowns from the HSfE to attribute this data at small population levels. The actual breakdown will be somewhat different and needs to be borne in mind as another source of potential error.

• Multiply the population cells by the corresponding prevalence to estimate the number of people in each cell with the disease

In mathematical notation:

Predicted log odds of prevalence = *b0* + *b1x1i* +  *b2x2 i* + *b3x3 i* +  *b4x4 I*

where *b0* = regression constant, *b1, b2,  b3, b4*= other regression coefficients

*x 1 i, x2 i, x3 i, x4 i* = value of risk factors for individual ***i***

(NB since all the variables are binary variables, x =1 if specified risk factor is present, x=0 if it is absent). Predicted log odds of prevalence for a community of n individuals is derived by averaging over the values for all individuals included in the community:

Predicted log odds of prevalence in community of n individuals:

= 1/*n* ∑i=1n (*b0* + *b1x1i* +  *b2x2 i* + *b3x3 i* +  *b4x4 i)*

= *b0* + *b1p1* +  *b2p2* + *b3p3* +  *b4pp4*

where p1 , p2, p3, p4=proportion of individuals in the community with characteristic x1 , x2 , x3 , x4 . (i.e. proportion with x.=1 rather than x.=0 as in the remainder).

The predicted prevalence for an individual is derived from their predictive log odds using:

prevalence = exp(log odds)/[1+exp(log odds)]

= *exp*(*b0* + *b1x1i* +  *b2x2 i* + *b3x3 i* +  *b4x4 i)/[1+* *exp*(*b0* + *b1x1i* +  *b2x2 i* + *b3x3 i* +  *b4x4 i)]*

Predicted prevalence in community of n individuals:

*= 1/n ∑i=1n[exp(b0 +b1x1i +b2x2 i +b3x3 i +b4x4 i)/[1+ exp(b0 +b1x1i +b2x2 i +b3x3 i +b4x4 i)]]*

Unfortunately, the equation above does not simplify to a linear combination of the predictor variables (in the way the mean log odds does). The average/overall prevalence is not the same as the prevalence for a person with “average” risk factors. So, for instance, it cannot be found by taking exp(log odds)/[1+ exp(log odds)] of the average log odds. There is no linear relationship with the regression coefficients, and with proportions of population with specified risk factors.

In order to find a synthetic estimate of prevalence, ideally we need to know the joint distributions of the included risk factors in the relevant population (the population on which are synthetic estimates are required). Ideally, we would know how many people in the population have each specific combination of risk factors. In practice, it might be good enough to know the distribution of some risk factors individually, rather than in combination. For instance, we might know what proportion of the population are smokers, and what proportion are ex-smokers, but not how many smokers we have by age and sex. In this situation, we have assumed that the same proportion of all ages and both genders are smokers and ex-smokers. Even if this is not exactly correct, then the synthetic estimate of prevalence may still be a reasonably accurate estimate (assuming that the smoking distribution does not vary too much by age, sex and other included risk factors). This is considered a good enough approach, and the best possible based on the information currently available in many cases.

In practice, we know the population distributions by age and sex, therefore we do not need to make the assumption that the proportion of males is the same for each age group. We use the more precise method of using the actual proportions of males in each age group. From the ELSA longitudinal survey we also know that older people/ older females in particular are generally less educated (on the basis of qualifications held). Therefore we apply the proportions with any educational qualifications according to age and sex group.

For other risk factors, we do not know whether these risk factors are more or less common in males than in females, nor according to age group, nor educational status i.e. we do not know their distributions in combination with any of the other risk factors included in the model. Therefore we make the assumption that the distribution of all other risk factors (apart from afore-mentioned age, sex and educational status), is equal across all other risk factors. This makes the calculations somewhat easier, even though this assumption might make for slightly less accurate estimates, the loss of accuracy is not thought to be great.

In order to find the estimated prevalence for each population, it is necessary to calculate the synthetic prevalence of risk factors for each possible combination of risk factor (as included in the chosen disease-specific logistic regression model). The estimated prevalence for a population is then the weighted average of the prevalence estimates for each combination of risk factors, according to the estimated number of people with each risk factor combination in the population (the population on which synthetic estimates are sought). These calculations can be carried out in Excel (using VBA code to link prevalence and risk factor spreadsheets with formulae in a workbook) or in Stata software to produce confidence intervals as well as the estimates.

We have developed two methods for producing small population estimates and associated CIs in Stata software. One uses a bootstrapping method to produce repeated samples (Method 1), the other (Method 2) uses inverse probability weights. Both methods produce CIs for the estimates, which are derived from the variance in the logistic model, not the local populations. It would have been useful to compare the results of both methods, but because of the short timeframe for this project we only used Method 2: Logistic regression and inverse probability weights.

### Method 1: bootstrapping procedure to produce repeated samples

The detailed methods of the Stata code we developed and used is included in Annex 1: synthetic estimation using Stata. In summary, within Stata, a new set of variables is created, one for each combination of these risk factors pertinent to the logistic regression model for the chosen disease. With our dataset set up in this way, we can now use Stata’s “predict” command to give us the predicted log odds. Then we find the weighted average of these, averaged across all possible combinations of risk factors, using the weights calculated as above (stored in variable named xyz). The weighted average can be found using the “collapse” command as follows, which results in one line of data per practice or MLSOA (using the population identifier as the by variable) in Stata.

We calculated in Stata CIs for prevalence estimates using a “bootstrap” procedure. There is uncertainty in these synthetic estimates of prevalence based on the imprecision not in the more usual sample of people from the population (since the estimates are not a sample but are externally applied), but in the estimated coefficients from the logistic regression equations. A bootstrap procedure can be used to construct confidence intervals on these synthetic estimates of prevalence, based on the imprecision in these logistic regression coefficients.

The philosophy underlying the bootstrap procedure is to consider that the people included in the data set used to derive the logistic regression equation represent the whole population of possible people. However, the whole population is effectively considered to contain thousands of copies of each of these people. Bootstrap samples are taken randomly from our initial populations (the subsets of the CPRD population that has complete data on appropriate risk factors). Logistic regression of the same risk factors can then be applied to this boot strap sample, i.e. we rerun the logistic regression that gave us our chosen predictive model. However, we get slightly different regression coefficients, because of the modified sample. Prevalence estimates are then derived for each combination of risk factors, based on these new regression equations.

This process is repeated 1,000 times, to find 1,000 different boot strap samples, by random sampling processes, and to then fit logistic regression equations on each. The prevalence estimates are calculated for each combination of risk factors, for each of these 1,000 boot strap samples. For each small population, a synthetic estimate is calculated for each boot strap sample, by appropriately weighting the prevalence estimates on each combination of risk factors (with the same weights as described above which reflect the anticipated prevalence of each combination of risk factors in the population). From these 1,000 synthetic estimates of prevalence of each population, a 95% confidence interval is calculated as the 2.5th to 97.5th centiles. Given that the estimates are distributed normally, these are taken to be mean +/- 1.96 SD (taking mean and SD of the 1,000 boot strap synthetic prevalence estimates for each specified region).

### Method 2: Logistic regression and inverse probability weights

Inverse probability weighting methods are used to standardise from a sampled population to a target population. They are usually defined as a function of a panel of one or more sampling-probability predictor variables. For each combination of the predictor variables, the sampling probability weight is the ratio of the frequency of that combination in the target population to the frequency of that combination in the sampled population. Inverse probability weighting is therefore a generalization of direct standardization. In Stata, it is implemented by using a *pweight* qualifier on an estimation command. This normally implies the use of a Huber variance formula to generate the confidence limits.

In a population case-control study, our sampled population is an exhaustive list of disease cases, plus a random sample of controls without the disease, with a known sampling fraction. The sampling probability weights are inversely proportional to the sampling fraction for each sub-population. For cases, the sampling probability weight is 1. And, for controls, the sampling probability weight is the reciprocal of the sampling fraction. (So, if the sampling fraction is 1/8, then controls are weighted upwards by a factor of 8.) These sampling-probability weights are used in logistic regression models. Predicted disease probabilities from these models will then be unbiased, if the model is correctly specified.

Similarly to Method 1 we estimated population parameters for logistic regression models. The risk factors in the model fell into two classes, namely always-present risk factors and sometimes-missing risk factors. The always-present risk factors were gender (Male or Female), age group (18-44, 45-64, 65-74 and 75+), ethnicity (White, Mixed, Black, Asian or Other, imputed to White if not known). The sometimes-missing risk factors were practice index of multiple deprivation (IMD) quintile (1, 2, 3, 4 or 5), smoking status (Non-smoker, Ex-smoker or Smoker), alcohol units per week category (None, (0,14], (14,42] or >42), and body mass index in kilos/square metre (BMI) category ((0, 18.5], (18.5,25], (25,30] or >30).

We fitted the logistic regression model, using Huber variances and sampling-probability weights. The parameters were a baseline odds for each of the 2x4=8 combinations of gender and age group, an odds ratio for each ethnicity except White, an odds ratio for each IMD quintile except the first, an odds ratio for each smoking status except Non-smoker, an odds ratio for each alcohol consumption category except Zero units, and an odds ratio for each BMI category except (18.5,25] kilos per square metre. The sampling-probability weights used were equal to the products of two sets of component sampling-probability weights. The first set of component weights standardised by case status from the case-control study sample to the denominator population from which the cases and controls were sampled, and were equal to 1 for RA cases (assumed to be sampled exhaustively from the cases in the CPRD denominator population), and equal in the controls to the reciprocal of the sampling fraction of the controls as a fraction of the non-cases in the CPRD denominator population (equal to 27.211693).

We also use inverse probability weights to correct for missing values as an easy-to-use alternative to multiple imputation. We then define the inverse probability weights using a completeness-propensity score. We have a panel of variables *V1…VK* that are always present (such as age and gender), and a panel of variables *U1…UJ* that are sometimes missing. Let C (for completeness) be the binary indicator variable indicating that all the variables *U1…UJ* are present. We then use a logistic regression model, regressing C with respect to the always-complete variables *V1…VK*. The completeness-propensity score is defined as the predicted completeness probability for each individual, under that regression model. The inverse-probability weight, for each individual with a complete set of data *U1…UJ*, is then the reciprocal of that individual’s completeness-propensity score. Therefore, individuals with a high probability of having complete data (like elderly females) are weighted downwards. And individuals with a low probability of completeness (like young males) are weighted upwards. These inverse-probability weights can then be used in further regression models, such as a logistic regression model to predict disease.

Therefore, the second set of component weights were computed to standardise the sample of cases and controls with all risk factors present to the total sample of cases and controls by gender, age group and ethnicity, and were derived as inverse probabilities of presence of the full set of risk factors (completeness) from a logistic regression model with completeness as the outcome, fitted to the cases and controls, using the first set of sampling-probability weights to standardise by case status, and whose parameters were a baseline odds for each of the 8 combinations of gender and age group and an odds ratio for each non-white ethnic category. The product weights therefore were computed to standardise the odds and odds ratios from the sample of cases and controls with all risk factors present (272,369 subjects out of a total of 101,870 cases and 440,293 sampled controls) to the total denominator population of subjects aged at or above 18 years, with or without RA, on their birthdays in 2015 (13,864,783 subjects). We also fitted logistic regression models of RA status with respect to the 8 combinations of gender and age only, using only the first set of sampling probability weights to standardise by RA status, in order to estimate odds (and thereby prevalence) of RA for each combination of gender and age group in the CPRD population at large.

Having estimated the regression model parameters, we used these for out-of-sample prediction of RA prevalence, using the *margprev* add-on Stata package [63 64]. These predicted prevalence estimates were for the sub-populations of patients for 7,692 practices, for 204 clinical care groups (CCGs), and for 6,755 MSOAs, for which information was available on the marginal frequencies of the seven risk factors in the model. We computed estimated prevalence assuming that, within each sub-population, the seven risk factors were mutually statistically independent, implying that we could give each possible combination of the seven risk factors a sampling-probability weight proportional to the product of the proportions of subjects with each of the appropriate risk-factor values. Therefore, for each subpopulation, we had 2x4x5x5x3x4x4=9600 combinations of risk factor values, with proportions of subjects calculated assuming statistical independence, and estimated the expected subpopulation prevalence of RA accordingly. The assumption of statistical independence of risk factors is probably not literally true, but might be expected to give prevalence estimates that are not vastly in error if the effects of the risk factors are not too non-additive. We have not internally or externally validated this method yet.

We have used method 2, logistic regression and inverse probability weights for these models because of the large number of variables in most of the models. This required us to produce Stata datasets of local risk factor data which have one observation for every permutation of all the risk factors for every practice, which generated very large files (up to 60 GB). We were able to process these using Stata/MP, the fastest and largest version of Stata. On dual-core chips, Stata/MP runs 40% faster overall and 72% faster on time-consuming estimation commands. It can handle a maximum number of 32,767 variables and 20 billion observations. Some of the datasets we used included over one billion observations. Processing was carried out on a multicore server. It would not have been possible to run the bootstrapping procedure to produce repeated samples which requires fitting a logistic model 1,000 times for each practice.

## Validation of local estimates

### Internal validation

In addition to the internal and external validation of the regression models, The local estimates can also be validated by aggregating them to the lowest geography available in the raw data and comparing them, a form of internal validation. These and external validations are shown in the Results. As noted above, we have over time increased the number of variables used in the local models as more local data has become available. However as more variables are added we need to take account of the joint effects of multiple risk factors, i.e. it assumes they operate independently. Estimation of the joint effects of multiple risk factors is complex for several reasons. In particular, some of the effects of more distal risk factors are mediated through intermediate factors. We have acknowledged this by creating specific joint distributions for variables where this is known e.g. age and educational level, as older age groups are less likely to have tertiary education.

### External validation

Because of the short timeframe for this project we have not had time to externally validate the local estimates using other similar datasets. However there are Quality & Outcomes Framework (QOF) disease registers[65] for all the models we produced here. We have experience in comparing QOF-registered prevalence and estimated prevalence right down to practice level using spatial analyses.[66] The local estimates can also be validated against the corresponding QOF register for each geography using Bland-Altman plots. This method uses graphical methods to investigate the assumptions of the method and also gives confidence intervals.[67] It aims to quantify the agreement between and clinical importance of two methods of clinical measurement using the differences between observations made using the two methods on the same subjects. The 95% limits of agreement, estimated by mean difference 1.96 standard deviation of the differences, provide an interval within which 95% of differences between measurements by the two methods are expected to lie. The second method is based on errors-in-variables regression in a classical (X,Y) plot and focuses on confidence intervals, whereby two methods are considered equivalent when providing similar measures notwithstanding the random measurement errors.[68] A recent update reconciles these two methodologies and shows their similarities and differences using both real data and simulations.[69]

# Results

## PAD prevalence from Whitehall II Data

Note that there 67% missing data for deprivation in Whitehall II data using Index of Multiple Deprivation (IMD). This is surprising since this is normally attributed using postcode of informants address, which the Whitehall II team must have. Table 1 shows missing data for key risk factor variables.

Table 17: missing data for key risk factor variables

|  |  |
| --- | --- |
| Risk Factor | Missing Values (%) |
| Age Group | 0 (0.0%) |
| Sex | 0 (0.0%) |
| Ethnicity | 0 (0.0%) |
| Hypertension |  |
| Dyslipidaemia |  |
| Family History (CHD) | 33 (0.3%) |
| Family History (Stroke) | 35 (0.3%) |
| Smoking | 12 (0.1%) |
| Obesity | 5 (0.04%) |
| Diabetes | 0 (0.0%) |
| Chronic Kidney Disease | 4242 (41.2%) |
| Hypercoagulation | 353 (3.4%) |
| Inflammatory markers | 1841 (17.9%) |
| Physical Activity | 3181 (6.7%) |
| Deprivation (IMD) | 6910 (67.0%) |

### Baseline characteristics of Whitehall II respondents

Table 17: Baseline Characteristics of Whitehall II definite PAD cases & controls

|  | PAD cases | No PAD | Total |
| --- | --- | --- | --- |
| Total Individuals (n) | 1.5% (n=152) | 98.5% (n=10156) | 100.0% (n=10,308) |
| Age (mean) | 69.7 | 67.3 | 67.3 |
| Age Group |  |  |  |
| 55-59 years | 0.6% (n=6) | 99.4% (n=994) | 9.7% (n=1000) |
| 60-64 years | 1.0% (n=30) | 99.0% (n=2981) | 29.2% (n=3011) |
| 65-69 years | 1.2% (n=27) | 98.8% (n=2309) | 22.7% (n=2336) |
| 70-74 years | 2.3% (n=49) | 97.7% (n=2101) | 20.9% (n=2150) |
| 75-79 years | 2.2% (n=40) | 97.8% (n=1771) | 17.5% (n=1811) |
| Ethnicity |  |  |  |
| White | 1.4% (n=130) | 98.6% (n=9051) | (n=9181) |
| Non-White | 2.0% (n=22) | 98.0% (n=1105) | (n=1127) |
| Sex |  |  |  |
| Male | 1.5% (n=104) | 98.5% (n=6791) | (n=6895) |
| Female | 1.4% (n=48) | 98.6% (n=3365) | (n=3413) |
| Hypertension |  |  |  |
| Yes | 2.2% (n=124) | 97.9% (n=5761) | (n=5885) |
| No | 0.6% (n=28) | 99.4% (n=4395) | (n=4423) |
| Dyslipidaemia |  |  |  |
| Yes | 1.7% (n=135) | 98.3% (n=7912) | (n=8047) |
| No | 0.8% (n=17) | 99.2% (n=2244) | (n=2261) |
| Diabetes |  |  |  |
| Yes | 3.5% (n=49) | 96.5% (n=1435) | (n=1394) |
| No | 1.2% (n=103) | 98.8% (n=8811) | (n=8914) |
| Obesity |  |  |  |
| BMI≥30 | 2.7% (n=57) | 97.3% (n=2040) | (n=2097) |
| BMI<30 | 1.2% (n=95) | 98.8% (n=8116) | (n=8211) |
| Smoking |  |  |  |
| Ever smoked | 1.7% (n=97) | 98.3% (n=5471) | (n=5568) |
| Never smoked | 1.2% (n=55) | 98.8% (n=4685) | (n=4740) |
|  |  |  |  |
| Chronic Kidney Disease |  |  |  |
| EGFR≤60 | 4.4% (n=30) | 95.6% (n=650) | (n=680) |
| EGFR>60 | 1.8% (n=99) | 98.2% (n=5287) | (n=5386) |
| Missing | 0.5% (n=23) | 99.5% (n=4219) | (n=4242) |
| Hypercoagulable state |  |  |  |
| Yes | 3.6% (n=80) | 96.4% (n=2161) | (n=2241) |
| No | 0.9% (n=72) | 99.1% (n=7995) | (n=8067) |
| Inflammatory markers |  |  |  |
| CRP≥3.0 | 2.7% (n=70) | 97.3% (n=2490) | (n=2560) |
| CRP<3.0 | 1.1% (n=82) | 98.9% (n=7666) | (n=7748) |
| Physical Activity |  |  |  |
| Low | 2.0% (n=46) | 98.0% (n=2203) | (n=2249) |
| Medium | 2.0% (n=23) | 98.0% (n=1156) | (n=1179) |
| High | 1.6% (n=58) | 98.4% (n=3641) | (n=3699) |
| Missing | 0.8% (n=25) | 99.2% (n=3156) | (n=3181) |
| Socioeconomic status |  | ` |  |
| Townsend 1st quintile | 1.1% (n=22) | 98.9% (n=1941) | (n=1963) |
| Townsend 2nd quintile | 1.4% (n=28) | 98.6% (n=1932) | (n=1960) |
| Townsend 3rd quintile | 1.6% (n=32) | 98.4% (n=1923) | (n=1955) |
| Townsend 4th quintile | 1.5% (n=29) | 98.5% (n=1940) | (n=1969) |
| Townsend 5th quintile | 1.7% (n=32) | 98.3% (n=1917) | (n=1949) |
| Missing | 1.8% (n=9) | 98.2% (n=503) | (n=512) |

## Whitehall II CVD definitions, incidence & prevalence

### Whitehall II prevalence

Prevalence of PAD in the Whitehall II data, broken down by age and sex, is shown in Table 18.

Table 18: Prevalence of PAD by age and sex from Whitehall II data

|  | Females | | | Males | | |
| --- | --- | --- | --- | --- | --- | --- |
| Age Group | PAD cases | Total number | Prevalence | PAD cases | Total number | Prevalence |
| 55-59 years | 2 | 284 | 0.7% | 4 | 716 | 0.6% |
| 60-64 years | 12 | 841 | 1.4% | 18 | 2170 | 0.8% |
| 65-69 years | 7 | 763 | 0.9% | 20 | 1573 | 1.3% |
| 70-74 years | 15 | 802 | 1.9% | 34 | 1348 | 2.5% |
| 75-79 years | 12 | 723 | 1.7% | 28 | 1088 | 2.6% |

## PAD regression modelling

### Univariate logistic analysis for PAD

Table 19 below shows the results for PAD of a univariate logistic model for individual risk factors and the outcome.

Table 19: univariate logistic model for individual risk factors for PAD

|  |  |  |  |
| --- | --- | --- | --- |
| Risk Factor | Odds Ratio (OR) | 95% CI | p-value |
| Age |  |  |  |
| 55-59 years | 1.00 | Reference |  |
| 60-64 years | 1.67 | [0.69-4.02] | 0.255 |
| 65-69 years | 1.94 | [0.80-4.71] | 0.144 |
| 70-74 years | 3.86 | [1.65-9.05] | 0.002 |
| 75-79 years | 3.74 | [1.58-8.86] | 0.003 |
| Sex |  |  |  |
| Male | 1.00 | Reference |  |
| Female | 0.93 | [0.66-1.31] | 0.686 |
| Ethnicity |  |  |  |
| White | 1.00 | Reference |  |
| Non-White | 1.39 | [0.88-2.19] | 0.161 |
| Hypertension |  |  |  |
| Normotensive | 1.00 | Reference |  |
| Pre-hypertensive | 0.92 | [0.64-1.32] | 0.639 |
| Hypertensive | 0.95 | [0.62-1.47] | 0.823 |
| Diabetes |  |  |  |
| No | 1.00 | Reference |  |
| Yes | 3.12 | [2.21-4.40] | <0.001 |
| Smoking |  |  |  |
| Never | 1.00 | Reference |  |
| Former | 1.59 | [1.13-2.25] | 0.008 |
| Current | 1.20 | [0.69-2.08] | 0.513 |
| Obesity |  |  |  |
| BMI < 18.5 | 1.00 | Reference |  |
| BMI 18.5-25 | 1.07 | [0.15-7.87] | 0.946 |
| BMI 25-30 | 1.91 | [0.26-13.87] | 0.523 |
| BMI 30-35 | 2.50 | [0.34-18.56] | 0.371 |
| BMI > 35 | 6.48 | [0.87-48.37] | 0.068 |
| Physical Activity |  |  |  |
| Low | 1.00 | Reference |  |
| Medium | 0.99 | [0.61-1.59] | 0.955 |
| High | 0.97 | [0.67-1.41] | 0.887 |
| HDL Cholesterol |  |  |  |
| > 1.55 g/L | 1.00 | Reference |  |
| 1.03-1.55 g/L | 1.04 | [0.74-1.47] | 0.807 |
| <1.03 g/L | 1.27 | [0.75-2.15] | 0.373 |
| LDL Cholesterol |  |  |  |
| <3.3 g/L | 1.00 | Reference |  |
| 3.3-4.1 g/L | 0.54 | [0.36-0.81] | 0.003 |
| >4.1 g/L | 0.33 | [0.19-0.55] | <0.001 |
| Triglycerides |  |  |  |
| < 1.7 g/L | 1.00 | Reference |  |
| 1.7-5.65 g/L | 0.94 | [0.63-1.39] | 0.751 |
| >5.65 g/L | 1.12 | [0.15-8.16] | 0.931 |
| CKD |  |  |  |
| EGFR > 60 | 1.00 | Reference |  |
| EGFR ≤ 60 | 2.28 | [1.50-3.46] | <0.001 |

Table 20 below show the results of multivariate model fitting for PAD (full model including all variables) except hypercoagulable state (OR 1.67 [4.15-7.75] p<0.001). Deprivation as measured by Townsend score was not significant.

Table 20: multivariable logistic regression model for PAD (full model including all variables)

| Risk Factor | Odds Ratio (OR) | 95% CI | p-value |
| --- | --- | --- | --- |
| Age |  |  |  |
| 55-59 years | 1.00 | Reference |  |
| 60-64 years | 2.77 | [0.83-9.31] | 0.099 |
| 65-69 years | 2.75 | [0.80-9.40] | 0.107 |
| 70-74 years | 4.68 | [1.41-15.58] | 0.012 |
| 75-79 years | 4.45 | [1.30-15.16] | 0.017 |
| Sex |  |  |  |
| Male | 1.00 | Reference |  |
| Female | 0.77 | [0.48-1.23] | 0.279 |
| Ethnicity |  |  |  |
| White | 1.00 | Reference |  |
| Non-White | 1.90 | [1.07-3.36] | 0.028 |
| Hypertension |  |  |  |
| No | 1.00 | Reference |  |
| Yes | 1.35 | [0.82-2.23] | 0.234 |
| Diabetes |  |  |  |
| No | 1.00 | Reference |  |
| Yes | 1.75 | [1.13-2.70] | 0.012 |
| Dyslipidaemia |  |  |  |
| No | 1.00 | Reference |  |
| Yes | 1.01 | [0.51-1.99] | 0.979 |
| Obesity |  |  |  |
| No | 1.00 | Reference |  |
| Yes | 1.38 | [0.89-2.12] | 0.156 |
| Smoker |  |  |  |
| Never | 1.00 | Reference |  |
| Ever | 1.62 | [1.07-2.45] | 0.023 |
| Chronic Kidney Disease |  |  |  |
| EGFR>60 | 1.00 | Reference |  |
| EGFR≤60 | 1.93 | [1.20-3.13] | 0.007 |
| Inflammatory Markers |  |  |  |
| CRP<3.0 | 1.00 | Reference |  |
| CRP≥3.00 | 1.66 | [1.11-2.49] | 0.014 |
| Physical Activity |  |  |  |
| Low | 1.00 | Reference |  |
| Medium | 1.05 | [0.58-1.88] | 0.878 |
| High | 0.85 | [0.53-1.36] | 0.494 |
| Socioeconomic Status |  |  |  |
| Townsend 1st quintile | 1.00 | Reference |  |
| Townsend 2nd quintile | 1.13 | [0.58-2.18] | 0.717 |
| Townsend 3rd quintile | 1.40 | [0.75-2.62] | 0.293 |
| Townsend 4th quintile | 1.47 | [0.77-2.80] | 0.243 |
| Townsend 5th quintile | 1.71 | [0.89-3.32] | 0.109 |

We then carried out stepwise forward and backward variable selection using likelihood ratios (LRs) and Wald tests because missing data had been imputed for some variables. Table 21 shows the final logistic regression model for PAD using stepwise forward and backward selection. Once again we have removed hypercoagulable state/on anticoagulants, which has an OR of 5.73, [4.23-7.79], p<0.001.

Table 21: logistic regression model for PAD (stepwise forward and backward selection)

| Risk Factor | Odds Ratio (OR) | 95% CI | p-value |
| --- | --- | --- | --- |
| Age |  |  |  |
| 70-74 years | 1.44 | [1.03-2.00] | 0.031 |
| 75-79 years | 2.11 | [1.53-2.91] | <0.001 |
| Sex |  |  |  |
| Male | 1.00 | Reference |  |
| Female | 0.66 | [0.47-0.93] | 0.016 |
| Hypertension |  |  |  |
| No | 1.00 | Reference |  |
| Yes | 1.67 | [1.19-2.35] | 0.003 |

As noted in the Methods, this final model above did not include a deprivation variable as it dropped out in the stepwise variable selection. However because deprivation is included in UK CVD predictive risk scores we produced a second set of local estimates including deprivation in order to check what effect this had on the estimates, even though it is not significant. So there are two sets of all local estimates, and these files are labelled with or without a deprivation variable. We used IMD in the final model (see Table 22 below) as it is the most commonly used deprivation score at the local level. Note that regression co-efficients are shown here rather than ORS- a positive coefficient means an OR>1 and vice versa.

Table 22: logistic regression full model for PAD with deprivation (IMD) score variable

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Odds ratio | Lower 95% CI | Upper 95% CI | p value |
| Age Group |  |  |  |  |
| 55-59 years | 1 | 1 | 1 | . |
| 60-64 years | 1.628 | 0.674 | 3.934 | 0.279 |
| 65-69 years | 1.757 | 0.720 | 4.286 | 0.216 |
| 70-74 years | 3.263 | 1.382 | 7.706 | 0.007 |
| 75-79 years | 2.954 | 1.233 | 7.081 | 0.015 |
| Sex |  |  |  |  |
| Male | 1 | 1 | 1 | . |
| Female | 0.787 | 0.548 | 1.130 | 0.195 |
| Ethnicity |  |  |  |  |
| White | 1 | 1 | 1 | . |
| Non-White | 1.236 | 0.764 | 2.000 | 0.387 |
| Diabetes |  |  |  |  |
| No | 1.000 | 1.000 | 1.000 | . |
| Yes | 2.349 | 1.640 | 3.364 | 0.000 |
| Smoker |  |  |  |  |
| Never | 1 | 1 | 1 | . |
| Ever | 1.383 | 0.983 | 1.946 | 0.063 |
| BMI |  |  |  |  |
| BMI <18.5 | 1 | 1 | 1 | . |
| BMI 18.5-25 | 1.044 | 0.141 | 7.728 | 0.966 |
| BMI 25-30 | 1.623 | 0.221 | 11.894 | 0.634 |
| BMI 30-35 | 2.766 | 0.376 | 20.364 | 0.318 |
| Chronic Kidney Disease |  |  |  |  |
| EGFR>60 | 1 | 1 | 1 | . |
| EGFR≤60 | 1.972 | 1.354 | 2.871 | 0.000 |
| Deprivation |  |  |  |  |
| IMD quintile 1 (least deprived) | 1 | 1 | 1 | . |
| IMD quintile 2 | 1.000 | 0.600 | 1.666 | 0.999 |
| IMD quintile 3 | 1.062 | 0.643 | 1.753 | 0.814 |
| IMD quintile 4 | 0.985 | 0.591 | 1.641 | 0.952 |
| IMD quintile 5 (most deprived) | 1.023 | 0.605 | 1.731 | 0.932 |
| \_cons | 0.003 | 0.000 | 0.023 | 0.000 |

## Internal validation

### ROC curves

We next examined the receiver operating characteristics (ROC) curves for the various models. The best ROC curve which predicts data perfectly will touch the top-left corner of the plot (area 1.0), and the larger the area under the ROC curve the better the prediction. An area of 0.5 signifies a prediction no better than chance. The results are summarised in Table 23.

Table 23: receiver operating characteristics (ROC) curves for the various CPRD models

| Model description | Model | ROC area | SE | 95% CI |
| --- | --- | --- | --- | --- |
| Logistic regression model for PAD including all risk factor variables (Full Model) | M3 | 0.6540 | 0.0083 | 0.6378-0.6702 |
| Logistic regression model for PAD – Forward and backward stepwise selection | M6 | 0.6478 | 0.0083 | 0.6316-0.6640 |

### Probability and sensitivity/specificity analysis

We used the stepwise forward models i.e. M3 and M6 to predict the probability of individual being a PAD case in the Whtehall II data set. We used box plots show the predicted probability of PAD caseness. Since we have a binary response model, we chose a cut-off point on the predicted probability to separate the predicted PAD cases from the predicted non-PAD cases (with lower predicted probability). No matter which cut-off point we choose, there will always be mis-classified people. Therefore, we used sensitivity and specificity plots to help with this decision.

The sensitivity/specificity versus probability cut-off plot shows us the corresponding sensitivity and specificity in each possible probability cut-off point (See **Error! Reference source not found.**). Higher sensitivity would usually yield low specificity and vice versa, the rule of thumb is to choose a cut-off probability to maximize both. We choose the cut-off probability where sensitivity and specificity lines cross.

## Local estimates

### Internal validation

We have not carried out a validation by aggregating local estimates because, as noted in the Methods, Whitehall II was not a nationally representative sample.

### External validation of practice estimates against QOF prevalence

The funding for the project does not include an in-depth external validation. For example, this could be carried out by obtaining an extract from a similar dataset e.g. applying the HSfE prevalence models’ equations to Whitehall II data. However another useful external data source is the Quality & Outcomes Framework (QOF) GP-diagnosed PAD prevalence. This can obviously be compared with diagnosed PAD prevalence from the model, taking into account that the Whitehall II definition was derived from the number of patients that reported being told by a nurse or doctor that they had PAD.

We carried out a disagreement analysis between model-estimated (without IMD score in the model) and QOF prevalence (%) of diagnosed PAD in practices. We estimated three principal components of disagreement (discordance as measured by Kendall's tau-a, bias as measured by median difference, and calibration as measured by the Theil-Sen median slope). Using the PAD estimates without IMD score in the model, the Kendall's tau-a between model-estimated and QOF prevalence of PAD for 7,496 practices was 0.286 (95% CIs 0.271-0.300), and p=0.000. Table 24**.** shows percentile differences between model-estimated and QOF prevalence of diagnosed PAD.

Table 24: percentile differences between model-estimated and QOF prevalence of PAD

| Percent | Percentile | (95% | CI) |
| --- | --- | --- | --- |
| 0 | -4.4 |  | -4.4 |
| 25 | 0.2 | 0.2 | 0.2 |
| 50 | 0.4 | 0.4 | 0.4 |
| 75 | 0.5 | 0.5 | 0.5 |
| 100 | 1.2 | 1.2 | 1.2 |

The best way to display the data is to plot the difference between the measurements by the two methods for each subject against their mean. This plot for practice-level PAD prevalence (Figure 1) shows explicitly the extent of agreement. In contrast to the plots for CHD and stroke, The difference between the estimates is not great, although in the majority of practices the estimated prevalence is higher. This is plausible if some patients with have a diagntsis made, but then change GP, or the current GP has told the patient they have PAD but does not record it on the PAD register, or if it is diagnosed in hospital or outpatients. The percentile slope of model-estimated prevalence with respect to QOF prevalence of diagnosed hypertension was 1.043 (95% CI 0.982-1.103). Figure 1 shows a Bland-Altman plot for model-estimated and QOF prevalence of diagnosed hypertension, and Figure 2 is a scatter plot of model-estimated and QOF prevalence of diagnosed hypertension.

Figure 1: Bland-Altman plot for model-estimated and QOF prevalence of xxx

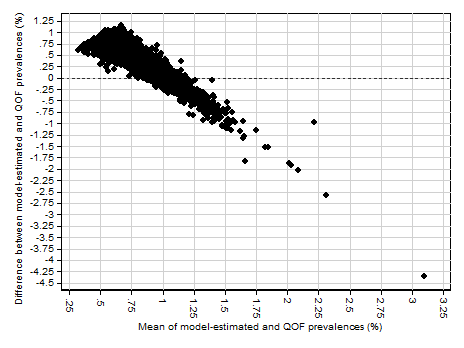
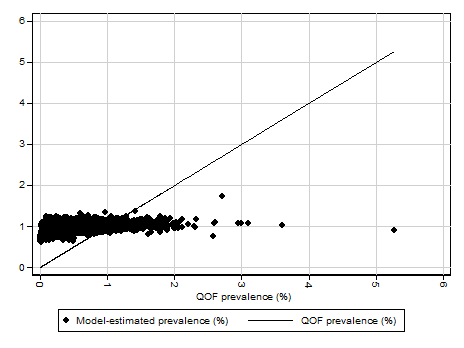


Figure 2: scatter plot of model-estimated and QOF prevalence of XXX



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