males (p>0.05, see figure). Our fully adjusted multivariate model showed that compared to white Europeans, South Asians had an ~2 fold increased hazard of developing CHD (HR, 1.83; 95% CI: 1.63 - 2.06, p < 0.0001) after accounting for age, gender, traditional cardiovascular risk factors, insulin resistance and related metabolic disturbances. We observed higher CHD incidence among South Asians compared to white Europeans, for each stratified age group (HRs 1.88, 1.86, 1.84, 1.67 for <45, 45–54, 55–65, >65 years, respectively, p<0.001).

Conclusion Our results provide robust evidence of an unexplained and two-fold higher incidence of CHD in South Asian males and females, compared to white Europeans, for all stratified age groups. Strikingly, the incidence of CHD in South Asian females was similar to that among European males. Our findings call for the discovery of novel biological pathways underlying high incident CHD in South Asians, to help understand and prevent CHD in this population, and to address a major NHS health inequality.

Conflict of Interest None

204 MACHINE LEARNING FOR INCIDENT CARDIO-RENAL-METABOLIC DISEASE AND CARDIOVASCULAR DEATH: THE OPTIMISE STUDY

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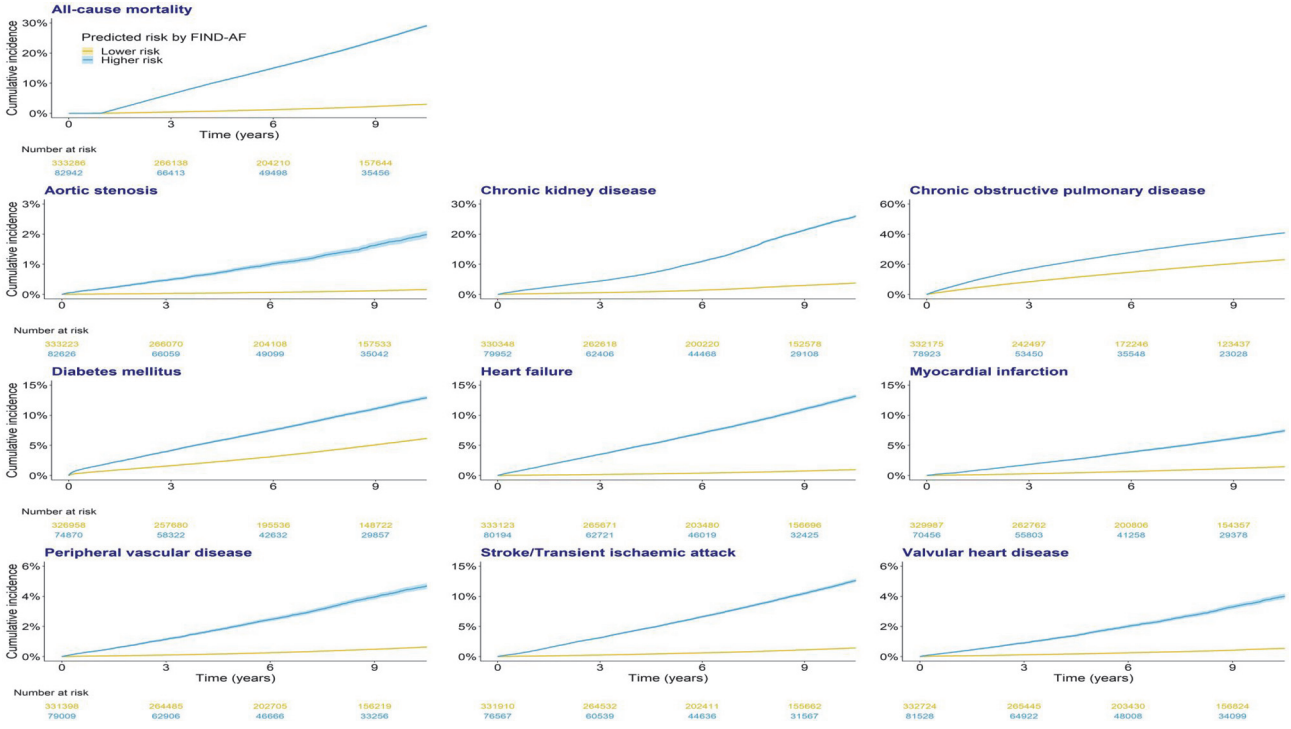
Introduction Cardiovascular disease (CVD) causes a quarter of all deaths in the UK,(1) and the NHS Long Term Plan emphasises that earlier detection and treatment of cardiovascular, renal and metabolic risk factors is a priority.(2) We trained, tested and prospectively implemented a machine learning algorithm in primary care electronic health record (EHR) data to identify individuals at higher risk of incident cardio-renal-metabolic diseases and cardiovascular death.(3, 4)

Methods We used UK primary care EHR data from 2 081 139 individuals aged ≥30 years (Jan 2, 1998, Nov 30, 2018), randomly divided into training (80%) and testing (20%) datasets. We trained a random forest classifier using age, sex, ethnicity and comorbidities. We calculated the cumulative incidence rate for ten cardio-renal-metabolic diseases and death, and excluded individuals for the analysis of each disease who had a preceding diagnosis of that disease. Fine and Gray's models with competing risk of death were fit for each outcome between higher and lower predicted risk.

We implemented the algorithm in a pilot interventional non-randomised single arm study (OPTIMISE) across six primary care sites. Consenting individuals aged ≥30 years at higher predicted risk received community-based cardio-renal-metabolic phenotyping and assessment for guideline-adherence of current treatment.

Results In the testing dataset (n = 416 228), individuals at higher predicted risk had higher long-term risk of heart failure (HR 12.54, 95% CI 12.08–13.01), aortic stenosis (9.98, 9.16–10.87), AF (HR 8·75, 95% CI 8·44–9·06), stroke/TIA (8.07, 7.80–8.34), chronic kidney disease (CKD) (6.85, 6.70–7.00), peripheral vascular disease (6.62, 6.28–6.98), valvular heart disease (6.49, 6.14–6.85), MI (5.02, 4.82–5.22), diabetes (2.05, 2.00–2.10) and COPD (2.02, 2.00–2.05) (figure 1). This cohort were also at higher risk of death (10.45, 10.23–10.68), accounting for 74% of cardiovascular deaths (8582 of 11676) during 10-year follow up.

Of 82 higher risk patients in the pilot clinical implementation (mean age 71.6 years (SD 7.5), 50% women), 78.0% had hypertension and 37.8% had type 2 diabetes (table 1). Of



Abstract 204 Figure 1 Kaplan-Meier plots for the ten cardio-renal-metabolic-pulmonary outcomes

Abstract 204 Table 1 Baseline characteristics of higher risk participants

	n (%)
Demographics	
Age, years (mean, SD)	70.9 (6.5)
Sex (women)	41 (50.0)
Body mass index, kg/m^2 (mean, SD)	30.1 (6.6)
Comorbidities	
Hypertension	64 (78.0)
Diabetes mellitus	31 (37.8)
Vascular disease	25 (30.5)
Chronic obstructive pulmonary disease	23 (28.0)
Chronic kidney disease	11 (13.4)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HDL, high density lipoprotein; LDL, low density lipoprotein, SGLT2, sodium-glucose co-transporter-2; SD, standard deviation.

Abstract 204 Table 2 Baseline investigations and medications for higher risk participants

	n (%)
Investigations	
HBA1c (mean, SD)	48.2 (10.2)
Estimated glomerular filtration rate (ml/min/1.73 m^2) (mean, SD)	72.8 (12.9)
urine albumin:creatinine ratio (mg/mmol) (mean, SD)	2.4 (2.5)
LDL cholesterol (mean, SD)	1.8 (1.1)
Medications	
Statin	54 (65.9)
ACE-i/ARB	41 (50.0)
SGLT2 inhibitor	4 (4.9)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HDL, high density lipoprotein; LDL, low density lipoprotein, SGLT2, sodium-glucose co-transporter-2; SD, standard deviation

higher risk patients with hypertension, 58.5% (31/53) of those aged <80 years had a systolic blood pressure (SBP)>140 mmHg, and 54.5% (6/11) of those aged ≥80 years had a SBP >150 mmHg. Of those with type 2 diabetes and co-existent CVD, only 23.1% (3/13) were on SGLT2 inhibitor therapy. Of higher risk patients on statin therapy, 37.0% (20/54) had LDL-cholesterol >1.8 mmol/L, and 23.1% (3/13) of patients with previous CVD had an LDL-cholesterol >2.0 mmol/L (table 2).

Furthermore, 19.5% (16/82) of the higher risk cohort had undiagnosed moderate or high risk CKD. Those with unrecognised CKD were often not on a statin (41.7%; 5/12), ACE-i/ARB therapy with co-existent hypertension (61.5%. 8/13), or an SGLT2 inhibitor with co-existent diabetes (50.0% (3/6), 83.3% (5/6), respectively). Almost half of the cohort (49%) were found to be obese, and 17% (14/82) were eligible for GLP-1 RA therapy.

Conclusions Machine learning can identify people at higher risk of cardio-renal-metabolic diseases and death in UK primary care EHR data. On prospective evaluation higher risk individuals have unrecorded and undertreated cardio-renal-metabolic diseases, which are actionable targets for integrated multi-disciplinary preventative care.

Conflict of Interest None

205 GENOME-WIDE SURVIVAL ANALYSIS OF 144,286 INDIVIDUALS IN THE UK BIOBANK IDENTIFIES NOVEL BLOOD PRESSURE LOCI

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Hypertension is a major heritable risk factor for cardiovascular disease worldwide. The genetic underpinning of hypertension has expanded to encompass over 1000 common single-nucleotide polymorphisms (SNPs) associated with the blood pressure phenotype. However, these SNPs explain only approximately 27% of the 30–50% estimated heritability of blood pressure. This suggests that, although they may individually have a small impact, there are still unidentified SNPs that play a role in influencing this trait. Conventional Genome-Wide Association Studies (GWAS) have traditionally relied on cross-sectional data, overlooking the dynamic temporal dimension inherent in disease development. This study is distinctive for utilising whole-genome data and departing from cross-sectional GWAS studies with binary outcomes to identify SNPs associated with hypertension development through a time-to-event analysis.

Disease outcome was determined based on data from various sources such as in-patient hospital records, self-reported data, primary care records, death registry data and time to event data collected in the UK Biobank. The timeframe for the survival analysis commenced from the enrolment of the final UK Biobank participant on October 1, 2010, and extended until the latest diagnosis of 'Essential hypertension' within the cohort on October 1, 2022, spanning approximately 12 years (4,383 days) of follow-up. For this analysis, samples containing whole-genome sequence (WGS) data were utilised. Employing the R package 'SPACox,' we conducted a genome-wide survival analysis utilising a saddlepoint approximation methodology rooted in a Cox Proportional Hazards (PH) regression model. SPACox facilitated genome-wide SNP association testing, with Age, Age2, Sex, BMI, and 10 principal components delineating population structure, included as covariates. Prior to the association analysis, stringent quality control (QC) measures were applied to the WGS data. SNPs exhibiting low call rates (<0.90), Hardy–Weinberg equilibrium exact test P-values below 1×10–15, or minor allele frequencies (MAFs) less than 0.01 were excluded from the analysis.

The analysis included 21,248 hypertension cases and 123,038 controls, totalling 144,286 participants, with 58.0% women (average age - 55.3±0.0279 years). Post-genotyping QC, 6,319,822 million SNPs underwent analysis, revealing 31 variants at genome-wide significance (P-value<5×10–08), including 29 novel SNP associations—15 in Fibrillin-2 (FBN2) and 4 in Junctophilin-2 (JPH2) genes. Subsequently, Mendelian randomization analysis, employing a 2-sample strategy, and utilising two identified SNPs (rs17677724 and rs1014754), suggested a causal relationship. Specifically, a genetically induced decrease in heart FBN2 expression and an increase in adrenal gland JPH2 expression were implicated in the elevation of blood pressure (P-Value =1.66×10–06, 3.19×10–06). Phenome-wide association (PheWAS) analysis using the FinnGen dataset (r9.finngen.fi) reaffirmed rs17677724's (β = 0.492, P = 7.4×10–09) and rs1014754's