Association of a sequence variant in DAB2IP with coronary heart disease

Seamus C. Harrison†, Jackie A. Cooper†, Kawaii Li†, Philippa J. Talmud†, Reecha Sofat‡, Jeffery W. Stephens§, Anders Hamsten¶, on behalf of the HIFMECH Consortium, Julie Sanders*, Hugh Montgomery†, Andrew Neil‡, on behalf of the Simon Broome Research Consortium, and Steve E. Humphries†

1BHF Laboratories, Department of Medicine, Centre for Cardiovascular Genetics, University College London (UCL), The Rayne Building, 5 University Street, London WC1E 6JF, UK; 2Division of Medicine, Centre for Clinical Pharmacology, University College London, Rayne Building, 5 University Street, London WC1E 6JF, UK; 3Diabetes Research Group, Institute of Life Sciences, Swansea University, Swansea SA2 8PP, UK; 4Cardiovascular Genetics and Genomics Group, Atherosclerosis Research Unit, Department of Medicine Solna, Karolinska Institutet, Centre for Molecular Medicine (L803), Karolinska University Hospital Solna, Stockholm S-17176, Sweden; 5Department of Epidemiology and Public Health, UCL, Gower Street Campus, London WC1E 7HN, UK; 6Institute for Human Health and Performance, UCL Archway Campus, Charterhouse Building, Highgate Hill, London N19 SLW, UK; and 7Division Public Health and Primary Health Care, University of Oxford, Oxford OX3 7LF, UK

Received 15 December 2010; revised 14 February 2011; accepted 23 February 2011; online publish-ahead-of-print 28 March 2011

Aims
A sequence variant, rs7025486[A], in DAB2IP on chromosome 9q33 has recently been associated with coronary heart disease (CHD). We sought to replicate this finding and to investigate associations with a panel of inflammatory and haemostatic biomarkers. We also sought to examine whether this variant, in combination with a chromosome 9p21 CHD variant (rs10757278) and the Framingham risk score (FRS), could improve the prediction of events compared with the FRS alone.

Methods and results
rs7025486 was genotyped in 1386 CHD cases and 3532 controls and was associated with CHD [odds ratio (OR) of 1.16, 95% confidence interval (CI) 1.05–1.29, P = 0.003]. Meta-analysis, using data from the original report and from genome-wide association studies in both the Wellcome Trust Case Control Consortium and the Cardiovascular Health Study, comprising 9968 cases and 20 048 controls, confirmed the association (OR of 1.10, 95% CI 1.06–1.16, 95% confidence interval (CI) 1.05–1.29, P = 3.2 × 10⁻⁶). There was no association with a panel of CHD biomarkers, including any lipid, inflammation, or coagulation trait, nor with telomere length. Addition to the FRS of this variant plus rs10757278 on chromosome 9p21 improved the area under the receiver-operating characteristic curve (AUC) from 0.61 to 0.64 (P = 0.03) as well as improving the reclassification (net reclassification index = 11.1%, P = 0.007).

Conclusion
This study replicates a previous association of a variant in DAB2IP with CHD. Addition of multiple variants improves the performance of predictive models based upon classical cardiovascular risk factors.

Keywords
DAB2IP • Coronary heart disease • Genetic • Single-nucleotide polymorphism • Genomics

Introduction
A recent genome-wide association study (GWAS) found a sequence variant in DAB2IP (rs7025486[A]) to be strongly associated with the presence of abdominal aortic aneurysm (AAA) with a per-allele odds ratio (OR) of 1.21 (P = 4.6 × 10⁻¹⁰).† The authors also found an association with early-onset myocardial infarction (MI) (OR 1.18, P = 3.1 × 10⁻⁵), MI at all ages (OR 1.08, P = 0.0012), peripheral arterial disease (PAD) (OR 1.14, P = 3.9 × 10⁻⁵), venous thrombo-embolism (VTE, OR 1.12, P = 0.0079), and pulmonary embolism (OR = 1.20, P = 0.00030) but not intracranial aneurysm or ischaemic stroke. This variant did not appear

* Corresponding author. Tel: +44 20 7674 6964, Fax: +44 20 7679 6212, Email: seamus.harrison@ucl.ac.uk
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to act through classical intermediate phenotypes such as smoking, lipids, obesity, type 2 diabetes (T2DM), and hypertension.

DAB2IP, located on chromosome 9q33, is a GTPase-activating protein thought to play an important role in prostate cancer metastasis. A single-nucleotide polymorphism (SNP) in this gene has been associated with aggressive prostate cancer, whereas in vitro functional studies have demonstrated that loss of the protein leads to enhanced cell proliferation and reduced apoptosis, via the PI3-Akt pathway. It is possible therefore, that this SNP exerts its effect by regulating cell senescence and proliferation. In 2007, three groups reported that another locus on the short arm of chromosome 9 at p21.3, tagged by the SNP rs10757278, was strongly associated with coronary heart disease (CHD). This SNP was also subsequently found to be associated with the risk of AAA and PAD but does not appear to act through classical intermediate phenotypes. There is mounting evidence to suggest that this SNP affects expression of the large non-coding RNA ANRIL, which in turn may affect expression of nearby genes such as the CDKN2A/B cluster which also play a role in cellular proliferation and senescence.

Methods

Study groups

Table 1 shows the baseline characteristics of each of the studies used. Ethics approval was granted for all studies. Detailed descriptions of each study are provided elsewhere. NPHS-II is a prospective study of healthy middle-aged men (50–64 years) recruited from nine UK general practices. In the 2742 Caucasian men with genotype data, by December 2009, there had been 272 CHD events comprising 175 acute CHD events (42 fatal), 74 coronary artery revascularization procedures, and 23 silent MI. The HIPMECH study compares male survivors of a first MI aged <60 years (excluding patients with FH and insulin-dependent diabetes mellitus) and population-based individuals of the same age and region recruited from four centres in Europe: Stockholm (Sweden) and London (England) for the North and Marseille (France) and San Giovanni Rotondo (Italy) representing the south. In all, a total of 598 post-infarction patients and 653 controls were included in the study. The Simon Broome Study recruited 409 patients with definite FH (all with a total cholesterol concentration of >7.5 mmol/L) with 127 definite CHD events as defined in Neil et al. The UDACS consists of 1014 consecutive subjects recruited from the diabetes clinic at the University of Leeds, UK. Patients with diabetes according to the WHO criteria and analysis was restricted to the Caucasian subjects with T2DM to remove possible heterogeneity within the sample. Coronary heart disease was defined in Wootton et al. The coronary artery bypass graft (CABG) patients were drawn from the coronary artery surgery inflammation study and are described elsewhere. Briefly, all patients undergoing elective first-time CABG at the Middlesex Hospital, London, UK, between October 1999 and September 2000 were invited to participate. Subjects undergoing additional surgical procedures (such as valvular surgery or aneurysmectomy), subjects with evidence of a pre-existing inflammatory state or unstable coronary artery disease, and subjects who suffered potentially confounding infective post-operative complications or circulatory failure requiring inotropic support were excluded. The CABG group includes 439 people (20% women) having different ethnic origin (83% Caucasians, 8% Asians, 2% Afro-Caribbean, 2% of other ethnicity, and 5% of unknown origin). Non-Caucasian subjects were excluded from the genetic analysis.

In silico analysis

The Cardiovascular Health Study is a longitudinal study of 3291 men and women, primarily of self-described European ancestry, who were free of clinical CVD at baseline, consented to the use of their DNA for cardiovascular research, and were successfully genotyped on the Illumina 370 CNV platform. There were 532 incident CHD events during follow-up. Data from the Cardiovascular Health Study GWAS of MI were accessed through a publicly available database (http://www.ncbi.nlm.nih.gov/gap). Data from the WTCCC of coronary disease were accessed, which included genotype data on 1988 CHD cases and 3004 controls from the National Blood Service and the 1958 Birth Cohort.

Genotyping

rs7025486 and rs10757274 were genotyped using TaqMan technology [Applied Biosciences, Warrington, UK]. Reactions were performed on 384-well microplates and analysed using ABI TaqMan 7900HT software (Applied Biosciences).

Measurement of telomere length

Leucocyte DNA was extracted by the salting-out method. Leucocyte telomere length was measured using a quantitative polymerase chain reaction (PCR)-based method as adapted in our laboratory. The relative telomere length was calculated as the ratio of telomere repeats to single-copy gene (SCG) copies (T/S ratio). For each sample, the quantity of telomere repeats and that of SCG copies were determined in comparison to a reference sample in a telomere an SCG quantitative PCR, respectively. All PCRs were performed in duplicate on the Rotor-Gene 6000 (Corbett Research Ltd, Cambridge, UK), and the raw data were analysed using the comparative quantification analysis (Rotor-Gene 6000 software, Corbett Research Ltd). The specificity of all amplifications was determined by melting curve analysis. Using the linear regression line between measures obtained by both the PCR-based method and the conventional terminal restriction fragment analysis for the same set of 32 samples, as previously described, the corresponding telomere length in base pairs (bp) was calculated from the T/S ratio measured in each subject.

Statistical analysis

Allele frequencies between groups were compared using \( \chi^2 \) test, and we tested for departure from the Hardy–Weinberg equilibrium in controls. Mean values for continuous variables were compared between those
Table 1  Baseline characteristics of studies

<table>
<thead>
<tr>
<th></th>
<th>UDACS</th>
<th>NPHS-II</th>
<th>Simon Broome</th>
<th>HIFMECH</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHD−, n = 358</td>
<td>CHD+, n = 135</td>
<td>P-value</td>
<td>CHD−, n = 2406</td>
<td>CHD+, n = 274</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.2 (10.9)</td>
<td>69.5 (9.9)</td>
<td>0.003</td>
<td>56.0 (3.4)</td>
<td>56.6 (3.5)</td>
</tr>
<tr>
<td>% male</td>
<td>56.4 (202)</td>
<td>69.6 (94)</td>
<td>0.008</td>
<td>100 (2406)</td>
<td>100 (274)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>142.0 (18.5)</td>
<td>137.9 (20.5)</td>
<td>0.03</td>
<td>136.8 (18.6)</td>
<td>141.4 (19.4)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.5 (10.9)</td>
<td>77.1 (10.5)</td>
<td>0.03</td>
<td>84.4 (11.2)</td>
<td>86.8 (11.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.2 (5.3)</td>
<td>29.5 (5.3)</td>
<td>0.54</td>
<td>26.2 (3.4)</td>
<td>26.6 (3.3)</td>
</tr>
<tr>
<td>% ever smokers</td>
<td>50.7 (173)</td>
<td>59.9 (79)</td>
<td>0.08</td>
<td>67.3 (1618)</td>
<td>77.7 (213)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.19 (1.06)</td>
<td>4.68 (1.11)</td>
<td>&lt;0.001</td>
<td>5.71 (1.01)</td>
<td>6.07 (1.02)</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.94 (1.10)</td>
<td>1.96 (1.08)</td>
<td>0.85</td>
<td>1.77 (0.93)</td>
<td>2.05 (1.07)</td>
</tr>
<tr>
<td>CRP (µg/L)</td>
<td>1.70 (1.41)</td>
<td>1.86 (1.59)</td>
<td>0.27</td>
<td>2.46 (2.43)</td>
<td>3.26 (3.33)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.70 (0.52)</td>
<td>2.80 (0.49)</td>
</tr>
</tbody>
</table>
with and without CHD using unpaired t-tests. Where necessary, variables were log-transformed before analysis and results are presented as geometric means with approximate standard deviations for these variables. Categorical variables were compared using $\chi^2$ tests. Genetic associations were tested using regression models using an additive (parallel) model. Hazard ratios (HRs) were calculated in the prospective study (NPHS-II), using Cox’s regression models with corresponding 95% confidence intervals (CIs). Odds ratios and their corresponding 95% CIs were calculated from case–control and cross-sectional studies using logistic regression models. Gene–disease associations were adjusted for age as a continuous outcome. In NPHS-II, analyses are stratified by general practice. For the conventional model, a score was derived based on age, triglycerides, cholesterol, smoking, and systolic blood pressure. We then fitted a model including both conventional factors and rs7025486 and rs10757274 genotypes and obtained a second score by weighting according to the $\beta$ coefficients from the model. The area under the receiver-operating characteristic (ROC) curve was calculated for both scores and the difference between the conventional model and that incorporating genotypes was tested. We assessed the effect of adding the genetic variables on the ability of the score to assign participants to the correct risk category using the net reclassification index (NRI). For meta-analysis of CHD outcomes, study-specific ORs and standard errors were obtained and pooled generating a summary estimate and its 95% CI. There was no evidence of between-study heterogeneity ($I^2 = 0\%$); therefore, a fixed-effects model was used. An additive model was used to confirm the association for additive effects found by Gretarsdottir et al. All analyses were carried out using Stata version 10 (Statcorp, TX, USA).

## Results

The characteristics of the study groups are presented in Table 1, which show the expected differences in classical risk factors in cases compared with controls and in baseline characteristics in those who subsequently went on to develop CHD in the prospective NPHS-II study. In the UDACS study, many risk factors are higher in the CHD-negative group, which is indicative of higher proportion cases being treated with statins and blood pressure-lowering medication. For both SNPs, the genotype distributions were as expected from the Hardy–Weinberg principles with the risk-allele frequency for the DAB2IP SNP rs7025486 ranging from 0.222 to 0.294 and for the Chr9p SNP rs10757274 ranging from 0.482 to 0.608.

### Association of rs7025486 with coronary heart disease

In each of the study groups, the rare allele was associated with 1.08–1.34 higher risk of CHD, although only one of these (CABG vs. healthy controls in NPHS-II) was nominally statistically significant using a $P$-value threshold of 0.05 (OR 1.2, 95% CI 1.03–1.46, $P = 0.021$). Pooled analysis of the results from each of the studies (Figure 1A) demonstrated that there was a consistent association between rs7025486 and CHD (OR 1.16, 95% CI 1.05–1.29, $P = 0.003$). Meta-analysis of data from the original report, the newly genotyped studies, and the WTCSS and CVHS GWAS data also demonstrated a consistent association (OR 1.1, 95% CI 1.06–1.14, $P = 3.2 \times 10^{-6}$), forest plot shown in Figure 1B.

### Conventional risk factors and coronary heart disease events

The baseline characteristics of the NPHS-II, stratified by subsequent CHD event, are presented in Table 1. The men who went on to develop CHD during follow-up ($n = 274$) were older, had higher plasma cholesterol, triglycerides, and blood pressure, and had lower HDL-cholesterol, and the prevalence of smoking was higher than in those who remained CHD free ($n = 2406$). On the basis of the measured variables included in the Framingham algorithm, the $AROC$ given by this set of classical risk factors (CRFs) was 0.61 (95% CI 0.572–0.651) (Figure 2). We created a simple additive ‘gene score’ (GS) based upon carriage of rs7025486 and rs10757278, combined with CRFs, to assess whether or not it would improve risk prediction and stratification compared with CRFs alone. There was no statistical evidence of interaction between these SNPs (see Supplementary material online, Table 3), and the $AROC$ for these two SNPs alone was 0.577 (95% CI 0.540–0.614). The $AROC$ for the model that included both CRFs and genotypes was 0.64 (95% CI 0.598–0.675; Figure 2), which was a small but statistically significant improvement when compared with the value achieved by CRFs alone ($P = 0.03$). The numbers of patients reclassified using the model that included CRFs and the two SNPs are shown in Table 2. The NRI was 11.1% which was statistically significant ($P = 0.007$). A Kaplan–Meier plot of freedom from CHD with increasing numbers of risk alleles carried is shown in Figure 3, demonstrating the added effect on risk of carriage of more than one risk allele.

### Discussion

This study is the first to replicate the association between rs7025486 and the risk of CHD following the initial publication.
SNPs with the largest effect and favourable MAFs (the so-called ‘low-hanging fruit’). Even meta-analysis of GWAS, involving many thousands of subjects, may be underpowered to detect all SNPs with modest effects sizes. Therefore, single SNP studies guided by the findings of GWAS are likely to be an important method to decipher which of the many associations that fail to reach genome-wide levels of significance are actually true positives.

Furthermore, although the fact that the effect sizes of newly discovered variants such as this are small, this does not preclude important biological insights being made. The fact that this variant has a similar effect in differing CHD aetiologies, and that there is no association with established biomarkers, implies that this variant is acting through pathways independent of those classically associated with CHD such as lipid metabolism. DAB2IP is involved in regulating cell survival and senescence, and the association seen here adds to emerging evidence (seen with the strong association between the 9p21 locus and CHD) that genetic variants in genes that regulate the cell cycle may be an important mediators of CVD. The additive effect on risk of CHD seen with these two SNPs implies that the accumulation of variants of modest effect in this pathway is an important independent mediator of CHD development (as suggested by the common variant hypothesis) and highlights potential targets for the development of novel therapeutic options.

The original report found an association with VTE and pulmonary embolism,1 so we hypothesized that this variant may act

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**Figure 1** (A) Meta-analysis studies genotyped in this paper for association between rs7025486 and coronary heart disease. Combined odds ratio (95% confidence interval) is 1.16 (1.05–1.29); P = 0.003. Fixed-effects additive genotype model. (B) Meta-analysis of association between rs7025486 and coronary heart disease, including newly genotyped, previously published data and genome-wide association study data from the WTCCC and CVHS. Odds ratio 1.10 (95% confidence interval 1.06–1.14, P = 3.2 × 10^-6). Fixed-effects additive genotype model.
through pathways that promote thrombosis but found no significant associations with a panel of haemostatic markers including fibrinogen, PAI-1, and numerous clotting factors. Shorter telomeres are associated with premature CHD; however, no consistent association between this SNP and mean LTL was found in 2012 subjects examined.

It is unlikely that a single SNP of modest effect will improve the prediction of CVD when compared with a risk score based upon multiple CRFs. It is much more likely, however, that variants found to be associated with CHD, which do not act through intermediate phenotypes such as lipid traits, which are already included in such risk scores, will be of use when combined with CRFs. It has been reported that addition of the single chromosome 9 SNP (rs10757278) to the FRS did not improve prediction (as measured by the $A_{ROC}$). In this study, we show that addition of two SNPs to the FRS improved the $A_{ROC}$ by 0.03 which was statistically significant ($P = 0.001$). Although the two SNPs show no statistical evidence of interaction, the study has limited power to detect such interactive effects, and possibly because of small numbers, risk was not highest in men carrying all four risk alleles. Such effects will need to be confirmed in larger studies. Because of the high frequency of both of the risk alleles, 38% of these UK men carry one risk allele, 34% carry two, and 14% carry three or four risk alleles, with those carrying two or more having an HR of over 1.7.

The $A_{ROC}$ is a commonly used statistic to describe the discriminative ability of a diagnostic test, but the number itself provides

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**Table 2** Reclassification based on the Framingham risk score + gene score

<table>
<thead>
<tr>
<th>Predicted CHD risk</th>
<th>Predicted CHD risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham + GS</td>
<td>Framingham + gene score</td>
</tr>
<tr>
<td>No. of individuals</td>
<td>Reclassified</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>Increased risk</td>
</tr>
<tr>
<td>5–10%</td>
<td>Decreased risk</td>
</tr>
<tr>
<td>≥20%</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Individuals without CHD during follow-up (n = 2009)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt;5%</td>
<td>89</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>297</td>
<td>371</td>
<td>3.7%</td>
</tr>
<tr>
<td>5–10%</td>
<td>134</td>
<td>769</td>
<td>240</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–20%</td>
<td>0</td>
<td>227</td>
<td>467</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20%</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals with CHD during follow-up (n = 216)</th>
<th></th>
<th></th>
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<th></th>
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<tbody>
<tr>
<td>0 to &lt;5%</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>45</td>
<td>29</td>
<td>7.4%</td>
</tr>
<tr>
<td>5–10%</td>
<td>3</td>
<td>65</td>
<td>27</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–20%</td>
<td>0</td>
<td>11</td>
<td>67</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20%</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>6</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Net reclassification improvement (95% CI) 11.1% (2.9–19.4)

The percentage correctly reclassified by adding gene score to the Framingham variables is 11.1% ($P = 0.007$). Green signifies correctly reclassified, yellow no reclassification and red incorrectly reclassified.
little clinically useful information. In the UK, the FRS is used to classify the population into risk groups that guide clinicians when planning treatment. In the UK, treatment with a statin is recommended in individuals with a 10-year risk >20%. In the NPHS-II at recruitment, adopting this policy would result in just 35 (1.6%) of men being offered treatment, in part because men with prevalent CHD or being treated with preventative medications were excluded. We found that addition of the two-SNP gene score to the FRS improved risk stratification as measured by the NRI of 11.1% (P = 0.007, 95% CI 2.9–19.4). If a policy was adapted whereby people with an FRS >20% or an FRS + GS >20% in the NPHS-II cohort were offered treatment, then the number of men who would qualify increases three-fold in the group who went on to develop CHD. It has been observed that the FRS tends to over-predict CVD in high-risk groups but under-predict CVD in low-risk groups. Compared with the general population, the participants in NPHS-II are a healthy cohort which is more clinically relevant NRI. Further research is required to assess whether or not these results are applicable on a population level.

Conclusion

This study has confirmed the effects of a common variant in DAB2IP (rs7025486) on the development of CHD. Prediction models which include CRFs and genotypes, which act through pathways independent of the CRFs, are likely to improve their performance. Even the small increment in AROC seen in this study has potential clinical utility when thresholds used for treatment in the UK are considered. Understanding the mechanism by which this variant exerts its effect should be the focus of ongoing research.

Supplementary material

Supplementary material is available at European Heart Journal online.

Acknowledgements

We acknowledge the contribution of the late Professor George Miller (1939–2006) who was the PI on the NPHS-II study and Phil Howard for his technical support. We also thank all the medical staff and patients who contributed to the NPHS-II study and the Office for National Statistics (NHS) Central Registry for provision of mortality data.

Funding

S.C.H. is supported by the BHF as a Chair Scholar, and S.E.H., J.A.C., and K.L. are funded by the British Heart Foundation (RG2008/08). Reecha Sofat is supported by a British Heart Foundation (Schillingford) Clinical Training Fellowship (FS/07/011). The NPHS-II study was supported by the Medical Research Council, the US National Institutes of Health (NIH 33014), and Du Pont Pharma. Diabetes UK supported J.W.S. (BDA: RD01/0001357) and the creation of UDACS. The HIFMECH study was supported by the European Commission (BMH4-CT96–0272), the Swedish Medical Research Council, the Swedish Heart–Lung Foundation, INSERM, Université de la Méditerranée (INSERM U626), Foundation pour la Recherche Médicale (FRM), and Programme de Recherche Hospitalier de Recherche (PHRC) 1996. HIFMECH co-investigators are A.H., S.E.H., Irene Juhan-Vague, Maurizio Margaglione, Giovanni di Minno, John Yudkin, and Elena Tremoli. We would like to thank the members of the Simon Broome BHF study for access to patients’ samples: Dr Rossi Naoumova, Prof. Gil Thompson, Dr Mary Seed, Prof. Paul Durrington, Dr Paul Miller, and Prof. John Betteridge. The Wellcome Trust Case Control Consortium was funded by the Wellcome Trust (076113/B/04/Z). Funding to pay the Open Access publication charges for this article was provided by the British Heart Foundation.

Conflict of interest: none declared.

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