Diabetologia (2014) 57:2513–2520
DOI 10.1007/s00125-014-3383-9

ARTICLE

Contrasting associations of insulin resistance with diabetes, cardiovascular disease and all-cause mortality in the elderly: PROSPER long-term follow-up

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Received: 17 June 2014 / Accepted: 29 August 2014 / Published online: 30 September 2014

Abstract

Aims/hypothesis Insulin resistance is commonly proposed as a precursor to both type 2 diabetes and cardiovascular disease (CVD), yet few studies have directly compared insulin resistance with both outcomes simultaneously and determined whether associations with each outcome differ in strength or are comparable. We assessed the association of fasting insulin and HOMA-IR with incident CVD and diabetes in older people.

Methods In the long-term follow-up of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) cohort, HOMA-IR measurement was available in 4,742 older people (70–82 years) without diabetes at baseline. Of these, 283 developed diabetes during the 3.2 year within-trial follow-up, while 1,943 all-cause deaths, 470 CHD deaths (identified from death records) and 590 fatal/non-fatal CVD events (identified from medical record linkage in the Scottish participants) occurred during an extended 8.6 years of total follow-up. Cause-specific Cox proportional-hazards models were fitted using multivariable models.

Results Higher HOMA-IR was associated with incident diabetes: HR 4.80 (95% CI 3.14, 7.33) comparing extreme thirds after adjustment for confounders. However, HOMA-IR in the top third was not associated with all-cause mortality, CHD mortality or fatal/non-fatal CVD: HR 1.02 (95% CI 0.90, 1.17), 1.03 (0.79, 1.36) and 0.94 (0.74, 1.20), respectively. Results were similar when fasting insulin was considered as an exposure.

Conclusions/interpretation Our data support insulin resistance as a predictor of diabetes in later life but, perhaps surprisingly, suggest this pathway is of negligible importance to CVD outcomes in the elderly.

Electronic supplementary material The online version of this article (doi:10.1007/s00125-014-3383-9) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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Keywords All-cause mortality · Cardiovascular disease · Insulin resistance · Risk factors

Abbreviations

CVD	Cardiovascular disease
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk trial

Introduction

The 'common soil' hypothesis of cardiovascular disease (CVD) and diabetes has given rise to widely adopted terms such as 'metabolic syndrome' and 'cardiometabolic risk factors'. While it is clear that diabetes is one of the strongest CVD risk factors [1], the extent to which moderate metabolic perturbations in advance of diabetes are associated with CVD appears weaker than previously appreciated [2–5].

It has been suggested that insulin resistance and its consequential compensating hyperinsulinaemia may be important steps in CVD pathogenesis. The possibility that hyperinsulinaemia promotes atherosclerosis is tempered by observations that insulin can be protective in some animal models [6], although insulin resistance itself is usually considered an adverse CVD phenotype. For instance, insulin resistance may act through inflammatory or endothelial dysfunction pathways to promote atherosclerosis [7]. Recent meta-analyses suggest the association of HOMA-IR and fasting insulin with CVD is likely to be modest, although many individual studies had limited power [8, 9]; for example, the most powerful study relating HOMA-IR to CVD had only 318 events during a 30 year follow-up [9]. Furthermore, the association of insulin resistance with CVD risk in the elderly, one of the most important groups in terms of current and future public health and population CVD burden, remains unclear because of the lack of relevant studies.

Using the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial cohort, we aimed to investigate the association of HOMA-IR with CVD and all-cause mortality in older people. HOMA-IR was also related to risk of in-trial diabetes as a secondary endpoint to verify that HOMA-IR was measuring propensity to develop diabetes and to compare and contrast HOMA-IR associations with diabetes versus vascular outcomes.

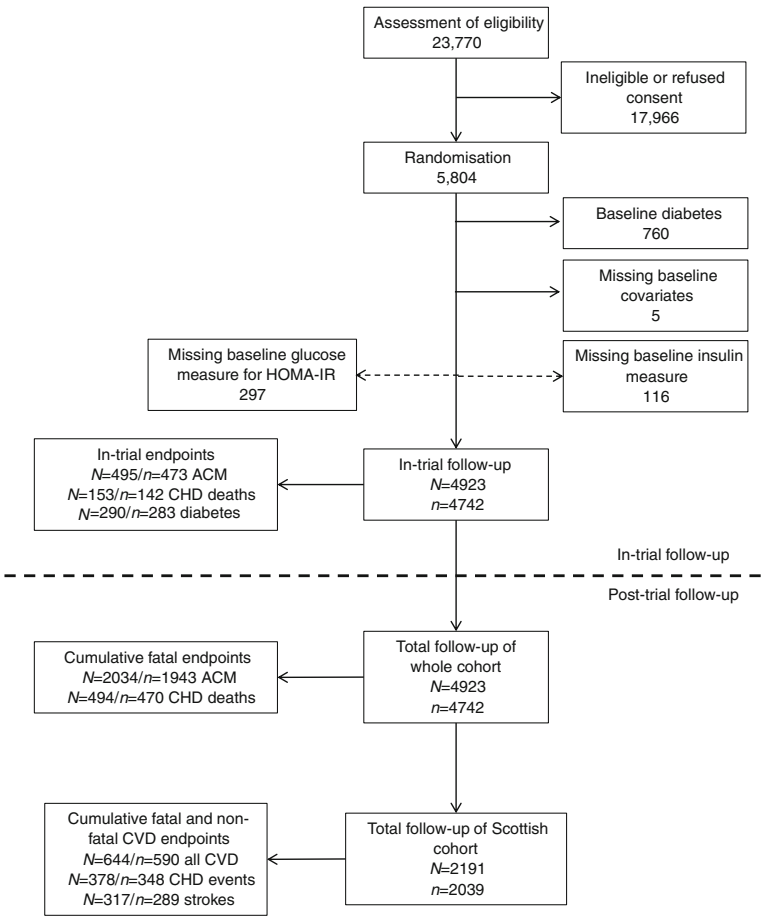

Fig. 1 Flow diagram for inclusion in PROSPER and data availability for the present study. *N* refers to number for fasting insulin exposure, and *n* refers to number for HOMA-IR exposure. ACM, all-cause mortality

Methods

Participants PROSPER was a randomised placebo-controlled trial designed to investigate the effect of pravastatin 40 mg on cardiovascular events in elderly participants (aged 70–82 years) with pre-existing or raised risk of CVD. Details of the original trial (3.2 years follow-up) and the long-term follow-up of PROSPER have been published [10, 11]. In brief, between December 1997 and May 1999 a total of 5,804 individuals were screened and enrolled in Scotland, Ireland and the Netherlands. Participants were asked to attend study visits after an overnight fast, venepuncture was performed, and separated plasma samples were stored at −80°C until assay. The institutional ethics review boards of all centres approved the protocol, and all participants gave written informed consent.

The present study excluded 760 participants with diabetes at baseline; cases of both known diabetes based on self-report and/or taking of oral hypoglycaemic agents and undiagnosed diabetes based on baseline glucose measurements (fasting blood glucose concentration ≥7.0 mmol/l or a glucose concentration of ≥11.1 mmol/l when fasting status was uncertain [<5%]) were excluded.

The primary outcome of the original trial was the composite endpoint of CVD, which included death from CHD, non-fatal myocardial infarction, and fatal or non-fatal stroke. All within-trial CVD events were adjudicated by a blinded independent review board [10, 12]. New-onset type 2 diabetes was diagnosed in the trial on the basis of a single elevated fasting plasma glucose result (≥7.0 mmol/l) or starting glucose-lowering therapy reported during in-trial study visits. The fatal endpoints presented in this analysis are based on events recorded during in-trial follow-up and then entirely by computerised record linkage during post-trial follow-up over an average of 8.6 years of total follow-up [11]. Incident diabetes over the extended follow-up is not available.

For Scottish participants, we were able to link to hospital discharge summaries held by the Information Services Division of the National Health Service for Scotland by means of established record-linkage methods as previously

Table 1 Baseline CVD risk factors by thirds of HOMA-IR

Baseline characteristic	Level	Thirds of HOMA-IR			*p* value
		T1 ≤1.37 (*N*=1,766)	T2 1.38–2.39 (*N*=1,675)	T3 ≥2.40 (*N*=1,301)	
Treatment allocation	Placebo	883 (50.0%)	845 (50.4%)	650 (50.0%)	0.95
Country	Scotland	668 (37.8%)	768 (45.9%)	603 (46.3%)	<0.0001
	Ireland	823 (46.6%)	586 (35.0%)	448 (34.4%)	
	Netherlands	275 (15.6%)	321 (19.2%)	250 (19.2%)	
Age	Years	75.43 (3.37)	75.36 (3.38)	75.31 (3.34)	0.63
Sex	Female	892 (50.5%)	892 (53.3%)	735 (56.5%)	0.0045
Current smoker	Yes	643 (36.4%)	434 (25.9%)	262 (20.1%)	<0.0001
BMI	kg/m^2	24.50 (3.35)	26.99 (3.60)	29.12 (4.19)	<0.0001
SBP	mmHg	152.8 (22.4)	154.5 (21.1)	155.2 (21.6)	0.0079
DBP	mmHg	82.6 (11.5)	84.2 (11.3)	84.3 (11.2)	<0.0001
HDL-cholesterol	mmol/l	1.41 (0.37)	1.28 (0.33)	1.17 (0.31)	<0.0001
LDL-cholesterol	mmol/l	3.80 (0.82)	3.88 (0.80)	3.79 (0.78)	0.0037
Triacylglycerol	Log mmol/l	0.16 (0.36)	0.34 (0.38)	0.54 (0.41)	<0.0001
History of hypertension	Yes	985 (55.8%)	1,088 (65.0%)	900 (69.2%)	<0.0001
History of CHD	Yes	558 (31.6%)	556 (33.2%)	448 (34.4%)	0.25
History of CVD	Yes	200 (11.3%)	203 (12.1%)	149 (11.5%)	0.74
History of peripheral vascular disease	Yes	207 (11.7%)	180 (10.7%)	140 (10.8%)	0.59
Diuretic use	Yes	610 (34.5%)	733 (43.8%)	663 (51.0%)	<0.0001
ACE inhibitor use	Yes	229 (13.0%)	270 (16.1%)	229 (17.6%)	0.0011
ARB use	Yes	33 (1.9%)	25 (1.5%)	32 (2.5%)	0.16
β-blocker use	Yes	428 (24.2%)	448 (26.7%)	371 (28.5%)	0.0253
CCB use	Yes	365 (20.7%)	464 (27.7%)	355 (27.3%)	0.0001

Values in parentheses are percentages or standard deviations

ARB, angiotensin receptor blockers; CCB, calcium channel blocker

described, thereby obtaining information on non-fatal CVD events [11]. For both deaths and hospital discharge summaries, data were available until 30 June 2008. Hence, for the analysis of composite fatal or non-fatal cardiovascular outcomes, our cohort is restricted to Scottish participants (n= 2,191 for the insulin analyses and n=2,039 for HOMA-IR analyses) (Fig. 1).

Lipids and glucose were measured as previously reported [10–13]. Insulin was measured using a commercially available ultrasensitive assay (Mercodia; Diagenics, Milton Keynes, UK) or, if the results were in excess of the limit of detection (140 pmol/l), by a standard sensitivity assay from the same manufacturer (n=65). The high-sensitivity assay had an intra-assay CV of 2.6% and an interassay CV of 6.2%, and the normal sensitivity assay had an intra-assay CV of 3.8% and an inter-assay CV of 7.2%. The exposure of interest in the present study was either fasting insulin or HOMA-IR calculated as: fasting plasma glucose (mmol/l) × insulin (pmol/l)/135.

Statistical methods Baseline characteristics were summarised as mean (SD) for continuous variables and as count (%) for categorical variables. Because of the non-normal distribution of insulin and HOMA-IR, logarithmic transformations were applied to these variables. The distribution of fasting insulin and HOMA-IR in the cohort was split into thirds, and related to risk factors of interest across the distribution using ANOVA. For the present study, only the first event was included as an endpoint for a given model (i.e. in the all CVD model, deaths preceded by a non-fatal event were excluded and participants were censored at the date of the non-fatal event). Years of follow-up were calculated from the date of randomisation until censoring due to end of the follow-up period, withdrawal of consent or death, whichever came first. Cause-specific Cox proportional-hazards models were fitted; we investigated both minimally and more fully adjusted models. In addition to the insulin or HOMA-IR variable, the minimally adjusted models also adjusted for the design variables of country and treatment randomisation (pravastatin or placebo). The more fully adjusted models further adjusted for relevant baseline risk factors (country, randomised treatment, age, sex, smoking status, BMI, systolic blood pressure, diastolic blood pressure, HDL-cholesterol and LDL-cholesterol, log triacylglycerol histories of CVD, medications that may affect HOMA-IR, diuretics, ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers). Tests for interaction were undertaken (ESM Methods). All statistical analyses were conducted in SAS version 9.2

Results

Among 5,044 participants without diabetes at baseline, data were available in 4,923 (97.6%) for fasting insulin and in 4,742 (94.0%) for HOMA-IR (Fig. 1).

HOMA-IR was positively associated with BMI and systolic and diastolic blood pressure, and was inversely associated with HDL-cholesterol. Women and non-smokers had higher levels of HOMA-IR. HOMA-IR was higher among participants from Scotland and the Netherlands, but there was no association with age or history of CVD (Table 1). Results for

Table 2 Association of fasting insulin and HOMA-IR with incident diabetes during in-trial follow-up

Variable/level	*N* participants	*n* events	Model 1			Model 2		
			HR	95% CI	*p* value	HR	95% CI	*p* value
HOMA-IR (per SD increase)	4,742	283	1.92	1.74, 2.13	<0.0001	1.69	1.50, 1.91	<0.0001
HOMA-IR T1	1,766	32	Ref	–		Ref	–	
HOMA-IR T2	1,675	92	3.09	2.06, 4.62		2.54	1.68, 3.85	
HOMA-IR T3	1,301	159	7.11	4.86, 10.4	<0.0001	4.80	3.14 ,7.33	<0.0001
Insulin (per SD increase)	4,923	290	1.62	1.48, 1.78	<0.0001	1.37	1.21, 1.54	<0.0001
Insulin T1	1,745	43	Ref	–		Ref	–	
Insulin T2	1,674	96	2.36	1.65, 3.39		1.81	1.25, 2.63	
Insulin T3	1,504	151	4.19	2.99, 5.88	<0.0001	2.43	1.65, 3.58	<0.0001

p value is for test for linear trend in HR estimates (across distribution)

Model 1 adjusted for country, randomised treatment

Model 2 additionally adjusted for age, sex, smoking status, BMI, systolic blood pressure, diastolic blood pressure, HDL-cholesterol, LDL-cholesterol, log triacylglycerols, histories of hypertension, coronary, cerebrovascular and peripheral vascular disease, diuretics, ACE inhibitors, angiotensin receptor blockers, β-blockers and calcium channel blockers

T1, lower third of the distribution; T2, middle third of the distribution; T3, top third of the distribution

fasting insulin were similar (ESM Table 1). HOMA-IR and fasting insulin were very strongly correlated (r=0.959, p<0.0001).

Associations of fasting insulin and HOMA-IR with risk of developing diabetes Over 3.2 years of within-trial follow-up, 283 participants were diagnosed with diabetes. Both HOMA-IR and fasting insulin were strongly associated with incident diabetes before and after adjustment for CVD risk factors and BMI (Table 2). In adjusted analyses, those in the highest third of HOMA-IR and fasting insulin were at 4.80 (95% CI 3.14, 7.33) and 2.43 (95% CI 1.65, 3.58) higher risk of developing diabetes, respectively (both p<0.0001). There was no strong evidence of interaction (ESM Fig. 1).

Associations of fasting insulin and HOMA-IR with risk of CVD events and mortality Over the 8.6 years of follow-up, there were 1,943 all-cause mortality events. In continuous models only adjusting for randomised treatment and country, both HOMA-IR (p=0.01) and fasting insulin (p=0.015) showed trends towards an inverse association with all-cause mortality, although these associations were attenuated to the null on further adjustment for other risk factors (Table 3). For CHD mortality and all CVD (fatal and non-fatal), neither

Table 3 Association of HOMA-IR and fasting insulin with all-cause mortality and CVD outcomes during total follow-up

Endpoint	Variable/level	*N* participants	*n* events	Model 1			Model 2		
				HR	95% CI	*p* value	HR	95% CI	*p* value
All-cause mortality	HOMA-IR (per SD increase)	4,742	1,943	0.94	0.89, 0.98	0.009	1.00	0.94,1.06	0.88
	HOMA-IR T1	1,766	759	Ref	–		Ref	–	
	HOMA-IR T2	1,675	655	0.86	0.77, 0.95		0.92	0.82, 1.03	
	HOMA-IR T3	1,301	529	0.89	0.80, 1.00	0.010	1.02	0.90, 1.17	0.14
	Insulin (per SD increase)	4,923	2,034	0.93	0.89, 0.98	0.003	0.99	0.94, 1.05	0.76
	Insulin T1	1,745	763	Ref	–		Ref	–	
	Insulin T2	1,674	661	0.86	0.78, 0.96		0.93	0.83, 1.04	
	Insulin T3	1,504	610	0.90	0.80, 1.00	0.015	1.03	0.91, 1.17	0.16
CHD mortality	HOMA-IR (per SD increase)	4,742	470	0.97	0.88, 1.07		0.96	0.86, 1.08	0.54
	HOMA-IR T1	1,766	167	Ref	–		Ref	–	
	HOMA-IR T2	1,675	178	1.10	0.89, 1.35		1.12	0.90, 1.41	
	HOMA-IR T3	1,301	125	1.00	0.79, 1.26	0.63	1.03	0.79, 1.36	0.56
	Insulin (per SD increase)	4,923	494	0.97	0.88, 1.06	0.46	0.97	0.87, 1.08	0.57
	Insulin T1	1,745	170	Ref	–		Ref	–	
	Insulin T2	1,674	166	1.00	0.81, 1.24		1.04	0.83, 1.30	
	Insulin T3	1,504	158	1.07	0.86, 1.33	0.77	1.15	0.89, 1.48	0.54
All CVD (Scottish cohort only)	HOMA-IR (per SD increase)	2,039	590	1.00	0.91, 1.09	0.99	1.01	0.91, 1.12	0.90
	HOMA-IR T1	668	185	Ref	–		Ref	–	
	HOMA-IR T2	768	238	1.08	0.89, 1.31		1.06	0.87, 1.30	
	HOMA-IR T3	603	167	0.95	0.77, 1.17	0.42	0.94	0.74, 1.20	0.50
	Insulin (per SD increase)	2,191	644	0.99	0.91, 1.08	0.82	0.99	0.90, 1.09	0.89
	Insulin T1	754	213	Ref	–		Ref	–	
	Insulin T2	782	245	1.09	0.90, 1.31		1.09	0.90, 1.32	
	Insulin T3	655	186	0.97	0.80, 1.18	0.47	0.98	0.78, 1.23	0.50

p value is for test for linear trend in HR estimates (across distribution)

Model 1 adjusted for country, randomised treatment

Model 2 additionally adjusted for age, sex, smoking status, BMI, systolic blood pressure, diastolic blood pressure, HDL-cholesterol, LDL-cholesterol, log triacylglycerols, histories of hypertension, coronary, cerebrovascular and peripheral vascular disease, diuretics, ACE inhibitors, angiotensin receptor blockers, β-blockers and calcium channel blockers

T1, lower third of the distribution; T2, middle third of the distribution; T3, top third of the distribution

HOMA-IR nor fasting insulin showed any trend towards an association either in minimally or fully adjusted models (Table 3 and Fig. 2). These results were consistent when the data were modelled using exposures as continuous variables to maximise statistical power (Table 3).

When effect estimates were stratified by within-trial follow-up versus post-trial follow-up, HRs were similar in both strata. There was also no strong evidence of interaction for the effect of insulin resistance by any covariate in the fully adjusted model for any endpoint (ESM Fig. 2 – ESM Fig. 4).

Discussion

During long-term follow-up of the PROSPER cohort of older people without diabetes, we observed no compelling evidence of an association of HOMA-IR with all-cause mortality, CHD mortality or CVD events over 8.6 years. By contrast, both fasting insulin and HOMA-IR were powerfully associated with risk for developing diabetes within the 3.2 years of in-trial follow-up, providing evidence of internal validity. Our results therefore suggest that insulin and insulin resistance are unlikely to be important CVD risk factors in elderly people without diabetes [6, 14, 15]. This is an important finding given that older people have been relatively poorly represented in studies to date but are an increasingly important group in public health terms. This is also consistent with a body of work across age ranges showing that many risk factors for CVD and diabetes are actually somewhat distinct [2–5]. Our work shows that, as with metabolic syndrome in the elderly [2], insulin resistance is a strong predictor of diabetes but has minimal prediction and therefore potential clinical relevance to vascular outcomes in the elderly.

Two recent meta-analyses have investigated the extent of the associations between insulin and HOMA-IR, and CVD [8, 9]. A study-level meta-analysis showed modest borderline significant associations between fasting insulin and CHD in those without baseline diabetes (OR comparing extreme thirds of the distribution was 1.12 [95% CI 0.98, 1.28], with moderate heterogeneity; I^2 59%) [8]. A more recent meta-analysis in people without diabetes showed, by comparing pooled standardised relative risks, that one standard deviation higher insulin (16 studies) and HOMA-IR (17 studies) were only modestly associated with CVD outcomes: risk ratios 1.13 (95% CI 1.05,1.22) (I^2 58.3%) and 1.25 (95% CI 1.16,1.35) (I^2 52.4%), respectively. Again, both meta-analyses demonstrated moderate heterogeneity. Our results in the elderly meaningfully extend these findings in a single powerful study including 1,943 all-cause mortality events and 470 CHD deaths.

The observational nature of this study means that causal inference (or inference of lack of causation) must be made with caution, although emerging data also support our results by lending at best weak support for a causal role of insulin resistance in CVD. Recent data from the Framingham Heart Study show that genetic variants near the IRS1 locus (associated with insulin resistance) are not associated with subclinical atherosclerosis [16]. Other recent trial evidence from the CAMERA randomised placebo-controlled trial of metformin in patients with CHD showed no reduction in carotid intima–media thickness with metformin compared with placebo [17],

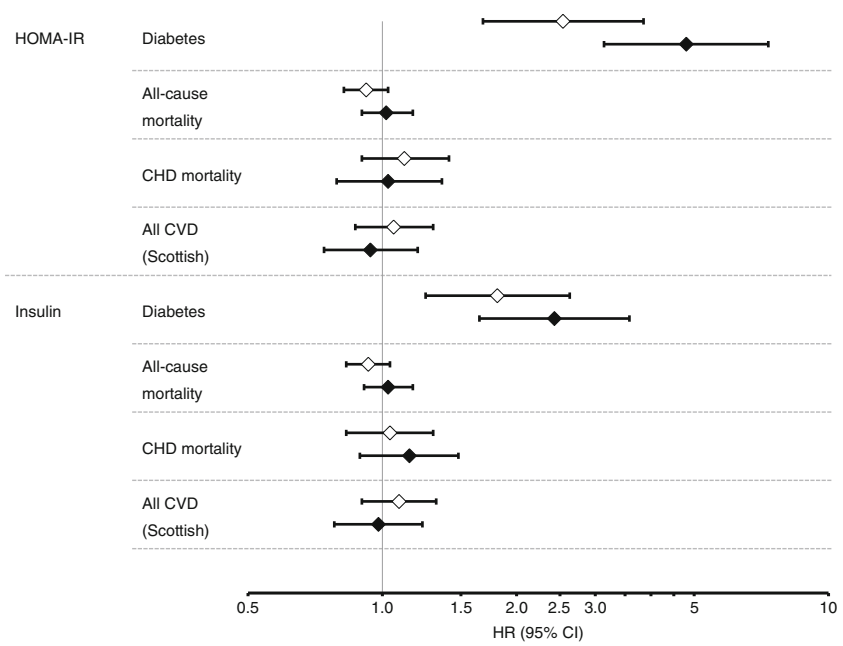

Fig. 2 Association of thirds of insulin and HOMA-IR with risk of endpoints. Diamonds refer to the point estimate for the HR comparing the middle third (open diamonds) or top third (black diamonds) with the bottom third of the distribution. Bars represent 95% CI; *x*-axis on the log scale

and metformin for 4 months also had no benefit on left ventricular function in patients after ST segment elevation myocardial infarction in another recent trial [18].

Fasting insulin and HOMA-IR are well-accepted surrogate measures of insulin resistance [19, 20], but are not gold standard measures of whole body insulin resistance, which is obtained by euglycaemic–hyperinsulinaemic clamping. It is a limitation of our study that we did not have such measures, although no large cohorts with prospective data that we are aware of have data on both insulin sensitivity measured by clamping techniques and sufficient numbers of CVD events to allow adequately powered statistical analysis. The multinational Relationship between Insulin Sensitivity and Cardiovascular Disease (RISC) Study recently reported weak cross-sectional associations of insulin sensitivity (measured by euglycaemic clamps) with carotid intima–media thickness in men but not in women, and, potentially more importantly, insulin sensitivity was not associated with 3 year changes in carotid intima–media thickness [21]. We also did not measure model-based insulin sensitivity or use data from OGTT; a recent meta-analysis suggests that correlation with euglycaemic-clamp-derived insulin sensitivity is $r=-0.60$ for log HOMA-IR, $r=0.57$ for model-based insulin sensitivity, and around $r=0.70$ for various OGTT-based measures [22]. An accompanying editorial suggests 'Where the focus is solely on insulin resistance…surrogate markers based on fasting samples alone are as valid as those that require multiple samples and an oral glucose load' [23].

Further potential limitations of the study require consideration. It is possible that our results may be influenced by the age of the PROSPER cohort; some risk factors are less strongly associated with CVD in older people. Although elderly, the PROSPER cohort represents a group of people in good cognitive health, and many other risk factors such as inflammatory markers have shown expected associations with CVD risk in this population [13, 24], and of course we show that insulin resistance strongly predicts diabetes. Older people are also an increasingly important age group in terms of public health and population CVD burden. It is also possible that insulin levels would be associated with increased cardiovascular risk over an even longer follow-up (than the 8.6 years studied here) given the period required for conversion into diabetes and then for those who have developed diabetes to accumulate CVD risk. However, this would suggest that diabetes is a CVD risk factor (i.e. hyperglycaemia per se), and not necessarily insulin resistance in the elderly without diabetes, and of course, diabetic patients also lose pancreatic insulin secretory capacity. Lack of availability of data on non-fatal CVD in the Irish and Dutch PROSPER participants during the extended follow-up limited the power of these analyses. Regardless, PROSPER remains one of the most powerful prospective studies relating HOMA-IR to CVD and is one of the very few to simultaneously relate it to incident diabetes.

In conclusion, our data support insulin resistance as a predictor of diabetes in later life but, perhaps surprisingly, suggest this pathway is of minimal/negligible importance to CVD outcomes in the elderly.

Acknowledgements We thank L. Cherry (Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK) for technical assistance.

Funding The study was supported by the Chief Scientist Office of the Scottish Executive Health Department who provided funding for long-term follow-up of the Scottish cohort: CZH/4/637. PW is supported by BHF fellowship FS/12/62/29889.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement AJC, JWJ, RGW, BMB, PMK, AB, DJS, IF and NS were involved in study design and conception. PW, DP and NS were involved in data acquisition. SML and IF conducted data analysis. PW, DP and NS wrote the first draft of the manuscript. SML, AJC, JWJ, RGW, BMB, PMK, AB, DJS and IF reviewed the manuscript for important intellectual content. All authors approved the final version for publication. NS and PW are responsible for the integrity of the work as a whole.

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