CLINICAL STUDY

Associations of IGF1 and its binding proteins with abdominal aortic aneurysm and aortic diameter in older men

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Abstract

Objective: Abdominal aortic aneurysm (AAA) is most prevalent in older men. GH secretion declines with age resulting in reduced IGF1 levels. IGF1 and its binding proteins (IGFBPs) are expressed in vasculature, and lower IGF1 levels have been associated with cardiovascular risk factors and disease. However, the relationship of the IGF1 system with aortic dilation and AAA is unclear. We tested the hypothesis that circulating IGF1 and IGFBPs are associated with AAA and aortic diameter in older men.

Design: A cross-sectional analysis involving 3981 community-dwelling men aged 70–89 years was performed.

Methods: Abdominal aortic diameter was measured by ultrasound. Plasma total IGF1, IGFBP1 and IGFBP3 were measured by immunoassays.

Results: After adjustment for age, body mass index, waist:hip ratio, smoking, hypertension, dyslipidemia, diabetes, coronary heart disease and serum creatinine, a higher IGF1 level was associated with AAA (odds ratio (OR)/1 s.d. increase 1.18, 95% confidence interval (CI) 1.05–1.33, $P=0.006$), as was the ratio of IGF1/IGFBP3 (OR = 1.22, 95% CI 1.10–1.35, $P<0.001$). Highest IGF1 concentrations compared with lowest quintile were significantly associated with AAA (quintile (Q) 5 vs Q1: OR = 1.80, 95% CI 1.20–2.70, $P=0.004$) as were IGF1/IGFBP3 ratios (Q5 vs Q1: OR = 2.52, 95% CI 1.59–4.02, $P<0.001$). IGF1 and IGFBP1 were independently associated with aortic diameter ($\beta=0.200$, 95% CI 0.043–0.357, $P=0.012$ and $\beta=0.274$, 95% CI 0.098–0.449, $P=0.002$ respectively).

Conclusions: In older men, higher IGF1 and an increased ratio of IGF1/IGFBP3 are associated with AAA, while IGFBP1 is independently associated with increased aortic diameter. Components of the IGF1 system may contribute to, or be a marker for, aortic dilation in ageing men.

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Introduction

Ageing is associated with a decline in pituitary GH secretion, resulting in reduced liver production of insulin-like growth factor 1 (IGF1) (1). IGF1 is a pleiotropic anabolic hormone, whose bioavailability is modulated by binding with IGF-binding proteins (IGFBPs) in the circulation (2). Most circulating IGF1 is carried within a ternary complex bound with IGFBP3 and the acid-labile subunit. IGFBP1 binds a smaller fraction of plasma IGF1, but does so in response to metabolic stimuli (3). Insulin suppresses hepatic IGFBP1 synthesis, decreasing the amount available for binding IGF1 and accounting for the association of reduced IGFBP1 with insulin resistance or the metabolic syndrome (4).

Abdominal aortic aneurysm (AAA) resulting from dilation of the abdominal aorta is a predictor of mortality

from aortic rupture and other manifestations of cardiovascular disease (CVD) (5, 6). Aortic diameter is a marker of global cardiovascular risk even in the absence of an AAA. Increasing age and male gender are key risk factors for AAA (7). IGF1, IGF1 receptors and IGFBPs are expressed in vascular smooth muscle cells (VSMC) of human atherosclerotic plaques (8), and lower circulating levels of IGF1 have been associated with the incidence of cardiovascular events and stroke in previous studies (9, 10). IGF1 concentration was reported to be decreased in human AAA tissue while concentrations of IGFBP1 and IGFBP3 were increased, raising the possibility that the IGF1 system contributes to the pathophysiology of AAA (11). However, an association between IGF1 status and the increased prevalence of AAA has never been examined in older men.

A reduced ratio of IGF1/IGFBP3 that may reflect a lower proportion of free or unbound IGF1 has been associated with metabolic syndrome (12). Therefore, we investigated the associations of plasma total IGF1, IGFBP1, IGFBP3 and the ratio of IGF1/IGFBP3 with AAA and aortic diameter in older men.

Methods

Study population

We studied subjects in the Health In Men Study (HIMS) that consists of a cohort of men who originally participated in a randomised controlled trial of screening for AAA (13). In 1996–1999, 12 203 community-dwelling men aged 65–83 years from Perth, Western Australia, attended for ultrasound screening for AAA. Each man completed a questionnaire assessing aspects of history and lifestyle relevant to AAA. In 2001–2004, 4263 men from the original cohort completed a follow-up visit; at that time an early morning blood sample was collected. The human research ethics committee of the University of Western Australia approved the study protocol and all men gave written informed consent before entering any part of the study.

Assessment of medical comorbidities

Medical comorbidity data were collected by questionnaire in 1996–1999 and reassessed in 2001–2004. Hypertension was defined as recorded blood pressure $\geq 140/90$, having a diagnosis of hypertension or receiving treatment for high blood pressure. Dyslipidaemia was defined as having high-density lipoprotein < 0.9 mmol/l; low-density lipoprotein ≥ 3.4 mmol/l; triglycerides ≥ 1.8 mmol/l or total cholesterol ≥ 5.5 mmol/l, or receiving lipid-lowering therapy. Diabetes was defined as having been diagnosed with or receiving treatment for diabetes, fasting glucose level, > 7 mmol/l or non-fasting glucose, > 11.1 mmol/l. Coronary heart disease (CHD) was defined by a history of myocardial infarction, angina, or treatment for coronary artery disease. Smoking history was categorised as current, ex-smoker or lifelong non-smoker. These risk factors were assessed at the time of blood sampling. Additional information on medical comorbidities was obtained from the Western Australian Data Linkage System which links together records from the Mental Health Information System, cancer register, death register and hospital morbidity data (14).

Measurement of abdominal aortic diameter

The greatest transverse and antero-posterior diameter of the infra-renal aorta was measured using a Toshiba Capasee ultrasound machine with a 3.75 MHz probe (Toshiba Australia, North Ryde, NSW, Australia). The

reproducibility of ultrasound measurements were assessed with 95% of measurement differences being < 3 mm, as previously reported (15). An AAA was considered present when the abdominal aortic diameter was ≥ 30 mm (5, 16).

Laboratory assays

Blood samples were collected between 0800 and 1030 h. Plasma was prepared immediately after phlebotomy and stored at -80°C until assayed. Hormone assays were performed as previously described (17). Briefly, total IGF1, IGFBP1 and IGFBP3 were assayed using reagent kits of single lot numbers from Diagnostics Systems Laboratories, Inc. (DSL, supplied by Beckman Coulter, Gladesville, NSW, Australia). The total IGF1, IGFBP1 and the IGFBP3 ELISA kits were used. The assays were automated using a Grifols Triturus ELISA processor (Vital Diagnostics, Castle Hill, NSW, Australia). For measurement of total IGF1, samples were pretreated with acid to displace IGF1 from binding proteins, followed by neutralisation and addition of binding inhibitors before assay. Between-run imprecision (coefficient of variation) was 12.2 and 8.6% at 117 and 216 ng/ml IGF1 respectively; 8.6 and 5.2% at 3.1 and 49 ng/ml IGFBP1 respectively; and 16.8 and 4.4% at 540 and 4300 ng/ml IGFBP3 respectively. All assays were carried out on freshly thawed aliquots of EDTA plasma in a series of runs performed between January 2008 and February 2009.

Statistical analysis

Data were analysed with the statistical package Stata, version 10.0 (StataCorp, 2007). Continuous variables were presented as mean $\pm$ S.E.M. and comparisons performed by Student's *t*-test. Nominal variables were presented as percentages (%) and compared with the χ^2 -test. Logistic regression analysis was used to assess odds ratio (OR) for AAA per a 1 S.D. increase in IGF1, IGFBP1, IGFBP3 or the ratio of IGF1/IGFBP3. Linear regression analysis was used to assess associations of IGF1, IGFBP1, IGFBP3 and IGF1/IGFBP3 with abdominal aortic diameter as a continuous variable. Regression analyses were adjusted for age, body mass index, waist:hip ratio, smoking, hypertension, dyslipidaemia, diabetes, CHD and serum creatinine as potential confounders. *P* values of < 0.05 were considered significant.

Results

IGF1, IGFBP3 and IGFBP1 levels in men with and without AAA

After excluding men for whom suitable plasma aliquots could not be retrieved and men with incomplete data, 3981 men were included in the analysis from the cohort

of 4263 (93.4%). Descriptive data from this cohort have been published previously showing that IGF1 and IGFBP3 levels were negatively correlated with increasing age, while IGFBP1 levels were positively correlated (17). Physical and biochemical variables of men with and without AAA are shown in Table 1. The mean time between assessment of AAA and subsequent blood sampling was 5.73 years (median 5.76 years, range 3.26–8.22 years).

Associations of IGF1, IGFBP1, IGFBP3 and IGF1/IGFBP3 with AAA

In univariate analyses, increased IGF1, IGFBP1 and the ratio of IGF1/IGFBP3 were each associated with increased OR for AAA (Table 2). In the fully adjusted logistic regression, a 1 s.d. increase in IGF1 level was associated with OR for AAA of 1.18 (95% confidence interval (CI) 1.05–1.33, $P=0.006$). Exclusion of non-fasted men did not alter this result (OR = 1.19, 95% CI 1.04–1.37, $P=0.012$), nor did exclusion of men with metabolic syndrome or diabetes (OR = 1.25, 95% CI 1.08–1.44, $P=0.003$). Neither IGFBP1 nor IGFBP3 were associated with AAA in the adjusted analysis. The ratio of IGF1/IGFBP3 remained associated with AAA in the fully adjusted model (OR = 1.22, 95% CI 1.10–1.35, $P<0.001$). Exclusion of non-fasted men did not alter this result (OR = 1.26, 95% CI 1.11–1.43, $P\leq 0.001$) nor did exclusion of men with metabolic syndrome or diabetes (OR = 1.21, 95% CI 1.07–1.38, $P=0.002$).

Distributions of AAA in each quintile of IGF1 and IGF1/IGFBP3 are shown in Table 3. In logistic regression analyses, IGF1 concentrations in the highest

quintile compared with the lowest quintile were significantly associated with AAA (OR = 1.80, 95% CI 1.20–2.70, $P=0.004$; Fig. 1A). Quintiles of IGFBP1 and IGFBP3 were not associated with AAA (Fig. 1B and C). Men with IGF1/IGFBP3 ratios in the highest two quintiles had increased odds of AAA compared with those in the lowest quintile (Q4 vs Q1: OR = 2.90, 95% CI 1.82–4.63 and Q5 vs Q1: OR = 2.52, 95% CI 1.58–4.02, both $P<0.001$; Fig. 1D). These results were not altered by exclusion of non-fasted men nor by exclusion of men with metabolic syndrome or diabetes (data not shown).

Associations of IGF1, IGFBP1, IGFBP3 and IGF1/IGFBP3 with aortic diameter

In univariate analyses, increased IGF1, IGFBP1 and the ratio of IGF1/IGFBP3 were each associated with increased abdominal aortic diameter (Table 4). Following adjustment for all other risk factors, only IGFBP1 and the ratio of IGF1/IGFBP3 remained associated. The coefficient for a 1 s.d. increase in IGFBP1 was 0.227 (95% CI 0.055–0.399, $P=0.010$). Exclusion of non-fasted men did not alter this result ($\beta=0.275$, 95% CI 0.079–0.471, $P=0.006$), nor did exclusion of men with metabolic syndrome or diabetes ($\beta=0.268$, 95% CI 0.067–0.468, $P=0.009$). For a 1 s.d. increase in IGF1/IGFBP3, the coefficient was 0.216 (95% CI 0.063–0.368, $P=0.006$). Exclusion of non-fasted men did not alter the result ($\beta=0.214$, 95% CI 0.037–0.392, $P=0.018$), nor did exclusion of men with metabolic syndrome or diabetes ($\beta=0.237$, 95% CI 0.066–0.409, $P=0.007$).

Multivariate models including IGF1 and IGFBP1, IGF1, and IGFBP3

In order to assess whether the association of IGF1 with aortic diameter was influenced by IGFBP1, a multivariate model including both IGF1 and IGFBP1 and the other covariates was constructed (Table 5). In the fully adjusted model, both IGF1 and IGFBP1 were independently associated with aortic diameter (coefficient for IGF1 was 0.200, 95% CI 0.43–0.357, $P=0.012$, for IGFBP1 0.274, 0.098–0.449, $P=0.002$). The results were similar after log-transforming aortic diameter (data not shown).

To assess whether the association of IGF1 with aortic diameter was independent of IGFBP3, both IGF1 and IGFBP3 were included in a multivariate model. The coefficient for IGF1 was higher compared with the adjusted model with IGF1 alone, and remained significant ($\beta=0.252$, 95% CI 0.063–0.442, $P=0.009$). The coefficient for IGFBP3 was lower compared with the adjusted model with IGFBP3 alone, but the CIs did not reach statistical significance ($\beta=-0.173$, 95% CI -0.365 to 0.018 , $P=0.076$).

Table 1 Physical and biochemical variables in community-dwelling older men compared according to the absence or presence of AAA. Continuous variables are presented as mean $\pm$ S.E.M. and compared with the two-sample *t*-test. Nominal variables are presented as percentages and compared with the χ^2 -test.

Characteristic	No AAA	AAA	P value
Number	3692	289	NA
Aortic diameter (mm)	21.7 $\pm$ 0.04	36.6 $\pm$ 0.45	<0.001
Age (years)	77.0 $\pm$ 0.06	78.3 $\pm$ 0.24	<0.001
BMI (kg/m ²)	26.5 $\pm$ 0.06	27.2 $\pm$ 0.22	0.003
WHR	0.97 $\pm$ 0.001	0.99 $\pm$ 0.004	<0.001
Non smoker (%)	35.0	11.6	<0.001
Previous smoker (%)	60.5	76.5	
Current smoker (%)	4.6	11.9	
Hypertension (%)	75.8	80.7	0.059
Dyslipidemia (%)	74.6	86.8	<0.001
Diabetes mellitus (%)	15.4	21.7	0.004
CHD (%)	41.0	69.2	<0.001
Creatinine (μ mol/l)	93.0 $\pm$ 0.5	106.1 $\pm$ 2.4	<0.001
IGF1 (ng/ml)	140.6 $\pm$ 1.0	152.2 $\pm$ 3.5	0.001
IGFBP1 (ng/ml)	26.6 $\pm$ 0.3	29.6 $\pm$ 1.5	0.054
IGFBP3 (ng/ml)	3.791 $\pm$ 15	3.705 $\pm$ 56	0.137
IGF1/IGFBP3	0.037 $\pm$ 0.0002	0.041 $\pm$ 0.0007	<0.001

WHR, waist to hip ratio; CHD, coronary heart disease.

Table 2 Four separate logistic regression models evaluating the associations of IGF1, IGFBP1, IGFBP3 and the ratio of IGF1/IGFBP3 with presence of AAA in community-dwelling older men.

	Univariate			Adjusted ^a		
	OR	95% CI	P value	OR	95% CI	P value
IGF1 (ng/ml)	1.19	1.07, 1.33	0.001	1.18	1.05, 1.33	0.006
IGFBP1 (ng/ml)	1.14	1.02, 1.27	0.019	1.07	0.94, 1.22	0.285
IGFBP3 (ng/ml)	0.91	0.81, 1.02	0.117	0.94	0.83, 1.07	0.363
IGF1/IGFBP3	1.25	1.13, 1.38	<0.001	1.22	1.10, 1.35	<0.001

OR, odds ratio of AAA being present for a 1 s.d. increase in the variable of interest; CI, confidence interval.

^aAdjusted for age, BMI, waist:hip ratio, smoking, hypertension, dyslipidemia, diabetes, coronary heart disease and serum creatinine.

Sensitivity analyses

Additional adjustment for height did not appreciably alter associations of IGF1 with AAA or aortic diameter (data not shown). Of the 289 men with AAA, 61 underwent AAA repair between 1996–1999 and 2001–2004. Excluding these men reduced statistical power, with IGF1 level no longer associated with AAA in the multivariate analysis (OR per a 1 s.d. increase 1.10, 95% CI 0.96–1.26). The ratio of IGF1/IGFBP3 remained associated with AAA in the adjusted analysis (OR = 1.17, 95% CI 1.04–1.31). In multivariate analyses, the associations of IGFBP1 and the ratio of IGF1/IGFBP3 with aortic diameter were attenuated ($\beta = 0.143$, 95% CI -0.0004 , 0.286 and $\beta = 0.125$, 95% CI -0.001 , 0.251 respectively). When both IGF1 and IGFBP1 were included in the multivariate model, IGFBP1 remained associated with aortic diameter ($\beta = 0.161$, 95% CI 0.015–0.308).

Discussion

In this study, we discovered that higher IGF1 levels or a higher ratio of IGF1/IGFBP3 were associated with increased odds of AAA. In addition, IGFBP1 was independently associated with increased aortic diameter. These findings were robust to adjustment for conventional risk factors, fasting status and prevalent metabolic syndrome or diabetes. The sensitivity analyses indicated that the ratio of IGF1/IGFBP3 was more closely associated with AAA than IGF1.

Lower circulating IGF1 has been associated with an increased risk of heart failure and occlusive atherosclerotic disease such as stroke and CHD (9, 10, 18). In several studies, lower IGF1 levels have also been associated with all-cause or CVD-related mortality (19, 20, 21). AAA and atherosclerotic CVD share common risk factors such as smoking and elevated blood pressure or cholesterol levels, and often co-exist. However, AAA and CVD may develop in parallel through different pathogenic mechanisms, with weakening of the aortic wall playing a key role in aortic dilation and AAA formation (7). Changes in the walls of aneurysmal aortas are characterised by up-regulation of proteolytic pathways, the loss of matrix, inflammation and, to a variable extent, atherosclerosis (22). In a study involving 115 cases of AAA, Lindholt *et al.* (23) recently showed that IGF1 levels are correlated with aneurysmal diameter and rate of progression. Our study extends this observation by demonstrating that higher level of IGF1 or the ratio of IGF1/IGFBP3 are associated with the presence of an AAA in a large cohort of community-dwelling older men.

Little is known about IGF1 activity in the walls of aortic aneurysms. A single previous study reported that IGF1 expression was reduced, while IGFBP1 and 3 concentrations were increased in aortic aneurysm tissue homogenates from ten patients who had surgery, compared with biopsies of normal aorta from ten organ donors, although it appears subjects were not matched for age and other risk factors making interpretation of this finding problematic (11). In animal models, increased IGF1 is associated with reduced degradation

Table 3 Quintile boundaries and distribution of men with AAA in each quintile of (A) IGF1 and (B) IGF1/IGFBP3. Numbers of men with AAA (%) and total number of men in each quintile are shown.

	Quintile				
	1	2	3	4	5
(A) IGF1 (ng/ml)	1.58–94.1	94.2–121	122–146	147–184	185–738
With AAA <i>n</i> (%)	44 (5.56)	59 (7.45)	47 (5.99)	61 (7.53)	78 (9.81)
Total <i>n</i>	791	792	784	810	795
(B) IGF1/IGFBP3	0–0.026	0.027–0.032	0.033–0.038	0.039–0.045	0.046–0.267
With AAA <i>n</i> (%)	26 (3.63)	42 (5.45)	51 (6.10)	82 (10.43)	88 (10.19)
Total <i>n</i>	716	770	836	786	864

Figure 1 Logistic regression analyses evaluating the associations of IGF1, IGFBP1, IGFBP3 and the ratio of IGF1/IGFBP3 with the presence of AAA in community-dwelling older men. Odds ratios are shown for quintiles of (A) IGF1, (B) IGFBP1, (C) IGFBP3 and (D) the ratio of IGF1/IGFBP3 with the lowest quintile (Q1) as the reference. Error bars are 95% confidence intervals. Analyses were adjusted for age, body mass index, waist:hip ratio, smoking, hypertension, dyslipidemia, diabetes, coronary heart disease and serum creatinine.

of extracellular matrix and reduced expression of matrix metalloproteinases (24). IGF1 stimulates collagen synthesis (25) and facilitates wound-healing (26), mechanisms that could protect against the development of AAA. Additionally, IGF1 may exert vascular effects by stimulating growth of VSMC (27, 28). Therefore, our results in a cohort of older men illustrate differences between animal models of AAA or acute vascular injury and repair (29), with the development of AAA *in vivo*. The IGF1/IGFBP system may exhibit complex effects on the vasculature, possibly via distinct actions of autocrine, paracrine and endocrine systems.

The contribution of a 1 s.d. increase in IGF1 level to the risk of having an AAA was limited with an 18% increase in risk. In older men, polymorphisms in the promoter region of the *IGF1* gene are a determinant of circulating IGF1 levels distinct from GH secretion (30). Of note the association of IGF1/IGFBP3 ratio with AAA and abdominal aortic diameter analysed as a

continuous variable was more prominent than that of IGF1 itself. A higher ratio of IGF1/IGFBP3 would be consistent with reduced binding of IGF1 to BP3, and a greater proportion of free or unbound IGF1 in the AAA group (2, 12). Thus in older men effects of the IGF1 system may be influenced by genetic factors and by IGFBP3, with higher circulating free IGF1 predisposing to aortic dilation or representing a more robust biomarker for AAA than total IGF1 levels.

Infra-renal aortic diameter is a predictor of mortality even below the threshold for diagnosis of AAA (5, 6). In our study, higher IGFBP1 was associated with abdominal aortic diameter and remained so after exclusion of non-fasting men, or men with metabolic syndrome or diabetes. When IGF1 and IGFBP1 were included in the multivariate model both remained associated with aortic diameter. Reduced IGFBP1 level has been associated with thickening of the carotid wall in patients with type 2 diabetes (31), and with metabolic syndrome in older men (17). Paradoxically, older adults with higher IGFBP1 levels experience increased all-cause and cardiovascular mortality despite the association of higher IGFBP1 with more favourable metabolic status (32, 33, 34). The association of higher IGFBP1 with aortic diameter is consistent with this counterintuitive concept and IGFBP1 may act independently of IGF1 on a cellular level to influence the vasculature (35). Additional investigation is required to assess mechanisms underlying the association of IGFBP1 with aortic diameter, and to clarify whether there is a causal relationship or whether IGFBP1 is a biomarker for adverse vascular outcomes in older men.

We have previously reported that lower free testosterone and higher LH levels were independently associated with AAA in this cohort of older men (36). This contrasts with this study where the higher IGF1 levels were associated with AAA, suggesting divergent pathways by which testosterone and IGF1 might influence AAA risk.

The strengths of this study include the large sample size, the standardised and reliable measurement of aortic diameter using ultrasound and the comprehensive adjustment for potential confounders in the multivariate analyses. Study limitations include the fact that blood testing was performed several years after baseline aortic diameter measurement. However, aortic diameter is relatively stable and the incidence of new AAA is very

Table 4 Four separate linear regression models evaluating the associations of IGF1, IGFBP1, IGFBP3 and the ratio of IGF1/IGFBP3 with abdominal aortic diameter in community-dwelling older men.

	Univariate			Adjusted ^a		
	β	95% CI	P value	β	95% CI	P value
IGF1 (ng/ml)	0.195	0.039, 0.351	0.014	0.152	−0.002, 0.305	0.053
IGFBP1 (ng/ml)	0.266	0.111, 0.422	0.001	0.227	0.055, 0.399	0.010
IGFBP3 (ng/ml)	−0.116	−0.272, 0.040	0.146	−0.026	−0.181, 0.129	0.743
IGF1/IGFBP3	0.329	0.173, 0.485	<0.001	0.216	0.063, 0.368	0.006

β , Regression coefficient per 1 s.d. increase in the variable of interest; CI, confidence interval.

^aAdjusted for age, BMI, waist:hip ratio, smoking, hypertension, dyslipidemia, diabetes, coronary heart disease and serum creatinine.

Table 5 Multivariate linear regression model evaluating associations of IGF1 and IGFBP1 with abdominal aortic diameter in community-dwelling older men. All covariates shown were included in the model and analysed according to a 1 s.d. increase for continuous variables, or the presence of a dichotomous risk factor.

	β	95% CI	P value
IGF1 (ng/ml)	0.200	0.043, 0.357	0.012
IGFBP1 (ng/ml)	0.274	0.098, 0.449	0.002
Age (years)	0.150	0.107, 0.194	<0.001
BMI (kg/m ²)	0.128	0.073, 0.182	<0.001
WHR	2.571	-0.094, 5.238	0.059
Previous smoker	0.886	0.559, 1.213	<0.001
Current smoker	2.980	2.266, 3.695	<0.001
Hypertension	-0.026	-0.386, 0.335	0.889
Dyslipidemia	0.220	-0.139, 0.579	0.229
Diabetes mellitus	0.013	-0.412, 0.439	0.951
CHD	0.954	0.637, 1.271	<0.001
Creatinine (μ mol/l)	0.013	0.008, 0.018	<0.001

β , regression coefficient; CI, confidence interval; WHR, waist to hip ratio; CHD, known coronary heart disease.

low ($\sim 0.4\%$ pa) (37), therefore the small number of interval cases of AAA is unlikely to have influenced the results. We did not have serial assessments of aortic diameter or blood samples for analysis, which restricts our ability to assess direction of causality. The cohort comprised men who returned for assessment and blood sampling from an earlier population-based sample (13). Therefore a 'healthy survivor' effect is possible which would make our results more conservative and applicable to generally healthier community-dwelling older men, and we cannot comment on associations in women. We did not have the capacity to measure free or unbound IGF1 levels either by immunoassay or ultracentrifugation, nor were we able to measure circulating IGF1 bioactivity (20). Therefore, our assessment was limited to circulating total IGF1, IGFBP1 and IGFBP3.

In conclusion, this study shows a positive association between circulating IGF1 or the ratio of IGF1/IGFBP3 with AAA, while IGFBP1 is independently associated with aortic dilation. IGF1 may have adverse effects in the aorta during ageing. If further studies replicate this observation, pre-clinical models may be required to assess the mechanistic basis for these associations.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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