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ARTICLE

Association of an *APOC3* promoter variant with type 2 diabetes risk and need for insulin treatment in lean persons

M. van Hoek · T. W. van Herpt · A. Dehghan · A. Hofman · A. G. Lieverse · C. M. van Duijn · J. C. M. Witteman · E. J. G. Sijbrands

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Abstract
Aims/hypothesis An *APOC3* promoter haplotype has been previously associated with type 1 diabetes. In this population-based study, we investigated whether *APOC3* polymorphisms increase type 2 diabetes risk and need for insulin treatment in lean participants.
Methods In the Rotterdam Study, a population-based prospective cohort (n=7,983), Cox and logistic regression models were used to analyse the associations and interactive effects of *APOC3* promoter variants (−482C>T, −455T>C) and BMI on type 2 diabetes risk and insulin treatment. Analyses were followed by replication in an independent case–control sample (1,817 cases, 2,292 controls) and meta-analysis.
Results In lean participants, the −482T allele was associated with increased risk of prevalent and incident type 2 diabetes: OR −482CT 1.47 (95% CI 1.13–1.92), −482TT 1.40 (95% CI 0.83–2.35), p=0.009 for trend; HR −482CT 1.35 (95% CI 0.96–1.89), −482TT 1.68 (95% CI 0.91–3.1), p=0.03 for trend, respectively. These results were confirmed by replication. Meta-analysis was highly significant (−482T meta-analysis $p=1.1\times10^{-4}$). A borderline significant interaction was observed for insulin use among participants with type 2 diabetes (−482CT*BMI p=0.06, −455TC*BMI p=0.02).
Conclusions/interpretation At a population-based level, the influence of *APOC3* promoter variants on type 2 diabetes risk varies with the level of adiposity. Lean carriers of the −482T allele had increased type 2 diabetes risk, while such an effect was not observed in overweight participants. Conversely, in overweight participants the −455C allele seemed protective against type 2 diabetes. The interaction of the variants with need for insulin treatment may indicate beta cell involvement in lean participants. Our findings suggest overlap in the genetic backgrounds of type 1 diabetes and type 2 diabetes in lean patients.

Keywords *APOC3* · BMI · Polymorphism · Type 1 diabetes · Type 2 diabetes

Abbreviations

ApoC-III	Apolipoprotein C-III
IRE	Insulin/phorbol ester responsive element
LPL	Lipoprotein lipase
RS1	Rotterdam study
RSPlus1	Rotterdam study plus 1

Introduction

Type 2 diabetes mellitus is characterised by overweight, impaired insulin secretion and insulin resistance [1]. Nevertheless, a substantial proportion of patients with type 2

M. van Hoek · T. W. van Herpt · E. J. G. Sijbrands (✉)
Department of Internal Medicine, Erasmus Medical Center,
PO Box 2040, 3000 CA, Rotterdam, the Netherlands
e-mail: e.sijbrands@erasmusmc.nl

M. van Hoek · A. Dehghan · A. Hofman · C. M. van Duijn · J. C. M. Witteman
Department of Epidemiology and Biostatistics,
Erasmus University Medical Center,
Rotterdam, the Netherlands

T. W. van Herpt · A. G. Lieverse
Department of Internal Medicine, Maxima Medical Center,
Eindhoven, the Netherlands

C. M. van Duijn
Department of Clinical Genetics, Genetic Epidemiology Unit,
Erasmus University Medical Center,
Rotterdam, the Netherlands

diabetes are lean [2, 3]. These patients would seem to suffer predominantly from impaired insulin secretion [4–6], whereas obese patients would be more resistant to insulin [7]. Defective insulin secretion has higher heritability estimates than insulin resistance in family and twin studies [8–10], and the concordance rate for type 2 diabetes in lean twins is higher than that in obese twins [11]. This suggests higher genetic susceptibility in lean type 2 diabetes and involvement of pancreatic beta cell dysfunction.

Lean type 2 diabetes has a number of similarities to type 1 diabetes. Interestingly, type 1 diabetes is more frequent in families with type 2 diabetes and vice versa [12, 13], a fact that supports the hypothesis of genetic overlap between the two diseases. In a paper by Hokanson et al., an *APOC3* haplotype determined by two promoter polymorphisms (−455T>C and −482C>T) was associated with type 1 diabetes [14]. Apolipoprotein C-III (ApoC-III) is an apolipoprotein involved in triacylglycerol metabolism. It inhibits lipoprotein lipase (LPL) and mediates lipoprotein uptake by the liver [15]. Higher ApoC-III production raises triacylglycerol and NEFA levels, and thus may affect beta cell function. [16, 17] On the other hand, ApoC-III has been suggested to directly bring on beta cell death [18]. Located in an insulin/phorbol ester responsive element (IRE), the promoter polymorphisms curb the capacity of insulin to downregulate the gene [19, 20]. In view of this evidence, we hypothesised that polymorphisms in the *APOC3* gene increase susceptibility of lean individuals to type 2 diabetes and that lean carriers of these polymorphisms with type 2 diabetes are more susceptible to insulin deficiency.

In the present population-based study, we investigated whether the *APOC3* −482C>T and −455T>C polymorphisms influence type 2 diabetes risk in lean persons. This was followed by replication testing in an independent sample. In addition, we investigated the associations with need for insulin treatment among type 2 diabetes participants from the Rotterdam Study (RS1).

Methods

Study population Details of the RS1 have been described elsewhere [21]. In brief, the RS1 was a prospective, population-based cohort study investigating determinants of chronic diseases in the elderly. A total of 7,983 inhabitants of a Rotterdam suburb, aged 55 years or older, were included. Baseline examinations were performed with follow-up measurements at 1–3 year intervals. Linkage to general practitioners' records provided continuous monitoring of major disease outcomes. Municipal health authorities regularly provided information on vital status.

In accordance with the guidelines of the ADA [21, 22] and WHO [23], diabetes was defined as a fasting plasma glucose level ≥7.0 mmol/l and/or a non-fasting plasma glucose level ≥11.0 mmol/l and/or treatment with oral glucose-lowering medication or insulin, and diagnosis of diabetes as registered by a general practitioner. Prevalent cases of diabetes were diagnosed at baseline by a non-fasting or post-load glucose level (after OGTT) ≥11.1 mmol/l and/or treatment with oral glucose-lowering medication or insulin, and by diagnosis of diabetes as registered by a general practitioner.

For the present study, general practitioners' records were searched for type 1 diabetes diagnoses and these participants were excluded. Data on insulin treatment were derived from interviews at baseline and the pharmacy database, which provided prospective data on prescribed insulin.

Written informed consent was obtained from all participants and the Medical Ethics Committee of the Erasmus Medical Center approved the study. For the present study, baseline data were collected between 1990 and 1993. Follow-up data were available until 1 October 2005.

Replication cohort The Rotterdam Study Plus 1 (RSPlus1) (290 cases, 2,292 controls) and the DiaGene study (1,527 cases) were used as a combined replication cohort (RSPlus1/DiaGene). RSPlus1 is an additional part of the prospective population-based RS1 and has been described in detail elsewhere [21]. The DiaGene study is an ongoing collection of type 2 diabetes cases and controls from the city of Eindhoven, the Netherlands. At the time of this replication effort, 1,527 DiaGene cases were available for genotyping. RSPlus1 and DiaGene cases were diagnosed according to the guidelines of the WHO [23] and ADA [21, 22], and/or based on treatment with oral glucose-lowering medication or insulin. RSPlus1 and DiaGene cases did not significantly differ in terms of age, sex and BMI, and were combined in the analyses.

Written informed consent was obtained from all participants and the Medical Ethics Committee of the Erasmus Medical Center approved the study.

Genotyping In the *APOC3* gene, the −482C>T(rs2854117) and −455T>C (rs2854116) promoter polymorphisms were chosen for genotyping on the basis of the ability to tag the variation previously associated with type 1 diabetes, and earlier associations with measures of glucose metabolism and localisation in an IRE [14, 24–26].

Genotyping was performed with TaqMan allelic discrimination assays designed and optimised by Applied Biosystems (Foster City, CA, USA). Reactions were performed on the TaqMan Prism 7900HT platform. The duplicates mismatch rate was 0.003 and 0.02 in the RS1 and 0.018 and 0.044 in the RSPlus1/DiaGene cohorts for the −482C>T and −455T>C polymorphisms, respectively. Genotype success rates for −482C>T and −455T>C were

0.95 and 0.94, and 0.96 and 0.97 in the RS1 and RSPlus1/DiaGene cohorts respectively.

Laboratory analyses In 3,930 participants fasting plasma samples were available at the second follow-up visit of the study for measurement of triacylglycerol. Triacylglycerol levels were measured by enzymatic colorimetric methods (CHOD-PAP and GPO-PAP; Boehringer Mannheim, Mannheim, Germany) on an analyser (Hitachi 911; Boehringer Mannheim).

Statistical methods Analyses were performed with SPSS software version 16.0 (SPSS, Chicago, IL, USA). Linkage disequilibrium was calculated with GOLD version 1.0. (http://www.sph.umich.edu/csg/abecasis/GOLD/, accessed 1 January 2007). Continuous variables are expressed as means ± SD. Comparisons between groups were performed with independent samples *t* tests and χ^2 tests for normally distributed continuous and categorical variables, respectively. Triacylglycerol levels were not normally distributed and therefore logarithmically transformed before the analyses. ANOVA was used for comparison of continuous variables between more than two groups. Deviations from Hardy–Weinberg equilibrium were assessed by means of χ^2 testing. Genotype frequencies were compared between incident and prevalent cases, and participants without type 2 diabetes.

In RS1, we tested the associations of the genotypes with type 2 diabetes and their interactions with BMI in logistic regression models and prospectively in Cox proportional hazards models for prevalent and incident type 2 diabetes, respectively. Participants with prevalent type 2 diabetes at baseline were excluded from the prospective analyses.

In the RSPlus1/DiaGene cohort we repeated the analyses described above using logistic regression. Haplotype analyses did not add any further information on analyses of the individual genotypes and are therefore not shown here.

To test the hypothesis of beta cell involvement, we tested the associations of genotypes with insulin treatment and their interactions with BMI in a logistic regression model in RS1 in patients with type 2 diabetes. Prevalent and incident insulin use was included in these analyses. Linear regression models were used to analyse the association between the polymorphisms and fasting triacylglycerol levels. All models were adjusted for year of birth and sex.

All analyses described above were repeated in two subgroups stratified for BMI using the RS1 population median. Lean persons had a BMI equal to or below 26 kg/m^2 and overweight persons had a BMI above 26 kg/m^2.

The *p* values found in RS1 and RSPlus1/DiaGene were combined by a *Z*-based meta-analysis using beta, standard error and number of participants of each cohort.

Combining RS1 and RSPlus1/DiaGene, we had 98% power to detect an effect of OR 1.3 (minor allele frequency 0.20) in the lean group (n=802 cases, i.e. the smallest group of cases analysed for type 2 diabetes).

Results

Baseline characteristics RS1 Diabetes status was available for 6,362 successfully genotyped persons. Participants whose genotyping was not successful or whose DNA was not available were 5.8 years older and included 8.5% more women. Nevertheless, the genotyped and not genotyped groups had similar distributions of BMI, waist circumference and presence of type 2 diabetes.

Participants with type 2 diabetes (prevalent and incident) had significantly higher BMI and waist circumference, and lower HDL-cholesterol, than those without type 2 diabetes (Table 1). Prevalent cases were significantly older and had significantly lower BMI than incident cases.

Population genetics In the total population and BMI subgroups, the polymorphisms were in Hardy–Weinberg equilibrium (χ^2<3.35, *df* 1, p>0.07). Heterozygosity for the −482 T allele was found in 34.6% of participants; 5.9% were homozygous. For the −455C allele these percentages were 43.0% and 12.6%, respectively. There was a strong linkage disequilibrium between the two polymorphisms, D'=0.968 (p<0.000001), r^2=0.54. Frequencies of genotypes did not differ significantly between participants with and without type 2 diabetes, or between incident and prevalent cases in the total population (data not shown).

We identified four haplotypes, H1 to H4, according to decreasing population frequency. H1 was defined by the absence of both minor alleles, H2 by the presence of both minor alleles, H3 by only the presence of the −455 minor allele and H4 by the presence of the −482 minor allele. The allele frequencies of H1, H2 and H3 were 64.4%, 23.4% and 11.8%, respectively.

Type 2 diabetes risk in lean and overweight persons In the total population, none of the genotypes significantly influenced the risk of type 2 diabetes. Adjustment for BMI and waist circumference did not change these results (data not shown).

We observed an effect of the interaction of −482C>T and −455T>C polymorphisms with BMI on prevalent type 2 diabetes (−482C>T*BMI, p=0.01; −455T>C*BMI p=0.01). Similar findings were observed prospectively for effect on the risk of incident type 2 diabetes (−482C>T*BMI, p=0.002; −455T>C*BMI, p=0.03).

Table 2 shows ORs for prevalent type 2 diabetes and HRs for incident type 2 diabetes according to *APOC3* promoter genotype in lean and overweight persons. In lean

Table 1 RS1 baseline characteristics of all participants and patients with and without type 2 diabetes

Characteristics	All participants	Without diabetes	Prevalent cases	Incident cases	*p* value
N	6,362	5,156	661	545	
Age (years)	69.4±9.1	69±9.1	73.5±9.2	68.4±7.9	<0.001[a,b]
Men (%)	40.6	40.4	39.5	44	NS
BMI (kg/m^2)	26.3±3.7	26.0±3.6	26.8±4.1	28.1±3.7	<0.001[a,b,c]
Total cholesterol (mmol/l)	6.6±1.2	6.6±1.2	6.5±1.2	6.6±1.2	NS
Triacylglycerol (mmol/l)	1.53±0.01	1.47±0.01	1.83±0.07	1.89±0.05	<0.001[a,c]
HDL-cholesterol (mmol/l)	1.34±0.37	1.37±0.37	1.25±0.37	1.25±0.34	<0.001[b,c]
Age at diagnosis (years)	NA	NA	68.6±0.50	74.8±0.34	<0.001[b]

Values are means±standard errors unless otherwise indicated

[a] For comparison between prevalent cases and participants without diabetes; [b] for comparison between incident cases and prevalent cases; [c] for comparison between incident cases and participants without diabetes

NA, not applicable

participants, the −482T allele was associated with increased risk of diabetes (−482CT OR 1.47, −482TT OR 1.40, p=0.009 for trend). Similar results were found in prospective analyses (−482CT HR 1.35 [95% CI 0.96–1.89], −482TT HR 1.68 [95% CI 0.91–3.1]; p=0.03 for trend). The −455T>C polymorphism showed similar associations in lean participants.

In overweight participants, no significant effects of the −482C>T polymorphism on diabetes risk was observed, while carriers of the −455C allele had lower prospective risk of type 2 diabetes (−455TC HR 0.88 [95% CI 0.71–1.1], −455CC HR 0.70 [95% CI 0.49–0.998], p=0.04 for trend).

Replication and meta-analysis Baseline characteristics of the RSPlus1/DiaGene cohort are shown in Table 3. Cases were older (p<0.001), had higher BMI (p<0.001) and were more often men (p<0.001) than controls. In the replication analyses, we found similar results to the original cohort, in

Table 2 HRs and ORs for incident and prevalent type 2 diabetes, replication and meta-analysis for *APOC3* genotypes in lean and overweight participants

Variants		RS1 HR			RS1 OR			Replication cohort			Overall
Polymorphisms per BMI	Genotype	Incident diabetes[a]	95% CI	*p* trend	Prevalent diabetes[a]	95% CI	*p* trend	OR[b]	95% CI	*p* trend	*p* value[c]
BMI≤26 kg/m^2											
−482C>T	CC	1.0			1.0			1.0			
	CT	1.35	(0.96–1.89)		1.47	(1.13–1.92)		1.06	(0.81–1.38)		
	TT	1.68	(0.91–3.1)	0.03	1.40	(0.83–2.35)	0.009	1.99	(1.25–3.16)	0.03	1.1×10^{-4}
−455T>C	TT	1.0			1.0			1.0			
	TC	1.27	(0.89–1.8)		1.65	(1.24–2.20)		0.86	(0.66–1.13)		
	CC	1.39	(0.85–2.28)	0.1	1.40	(0.92–2.13)	0.01	1.09	(0.74–1.62)	0.9	0.04
BMI >26 kg/m^2											
−482C>T	CC	1.0			1.0			1.0			
	CT	1.04	(0.84–1.28)		0.85	(0.66–1.10)		1.04	(0.88–1.23)		
	TT	0.56	(0.32–0.98)	0.3	0.84	(0.51–1.39)	0.22	1.47	(1.08–1.99)	0.05	0.73
−455T>C	TT	1.0			1.0			1.0			
	TC	0.88	(0.71–1.1)		0.98	(0.76–1.25)		0.90	(0.76–1.06)		
	CC	0.70	(0.49–0.998)	0.04	0.71	(0.48–1.06)	0.16	0.79	(0.62–1.02)	0.05	0.003

[a] Adjusted for year of birth and sex

[b] Adjusted for age and sex

[c] Meta-analyses p value combining RS1 and RSPlus1/DiaGene

Table 3 Baseline characteristics from the RSPlus1/DiaGene sample

Characteristics	All participants [a]	Controls	Cases	*p* value
n	4,134	2,292	1,817	
Age (years)	65.5±9.0	64.4±7.8	66.8±10.1	<0.001
Men (%)	48.4	44.3	53.7	<0.001
BMI (kg/m^2)	28.4±4.9	26.9±3.9	30.4±5.3	<0.001

Unless otherwise shown, values are means ± standard error

[a] Diabetes status missing for 25 participants

which the −482T allele increased type 2 diabetes risk in lean persons (−482CT 1.06 [95% CI 0.81–1.38], −482TT 1.99 [95% CI 1.25–3.16]; p=0.03 for trend). No significant effects were found for the −482C>T and −455T>C polymorphisms in overweight participants (p=0.05 for trend for both).

In meta-analyses, the effect of the −482T allele in lean participants was confirmed ($p=1.1\times10^{-4}$ in meta analysis). In overweight participants, a protective effect of the −455C allele seemed to be present (p=0.003)

Insulin treatment in lean and overweight participants Table 4 shows the ORs for insulin treatment among participants with diabetes, according to the −482C>T and −455T>C genotypes. None of the ORs was statistically significant in this small group of participants. However, there was a borderline significant interaction of the −482C>T polymorphism with BMI in participants with diabetes (−482C>T*BMI, p=0.06) and a significant interaction for the −455T>C polymorphism (−455T>C*BMI, p=0.02).

Intermediate traits The genotypes were not associated with BMI (−482C>T, p=0.60; −455T>C, p=0.21) or fasting triacylglycerol levels (−482C>T, p=0.67; −455T>C, p=0.73). They were also not associated with fasting triacylglycerol levels within the high and low BMI groups (data not shown).

Discussion

Main findings In this population-based study, we found significant interactions between BMI and genetic variants in the *APOC3* promoter for type 2 diabetes risk. Lean participants carrying the −482T allele had higher risk of type 2 diabetes. These results were replicated in an independent population. Moreover, *APOC3* promoter variants showed a borderline significant interaction with BMI for the need for insulin therapy. Presence of the minor alleles showed a trend towards increased need for insulin therapy in lean participants. Conversely, in overweight participants the −455C allele seemed protective against type 2 diabetes.

The RS1 study design included meticulous follow-up on disease outcomes over a long time. The large number of diabetic cases enabled us to replicate the findings within our population in prevalent and incident cases. Moreover, we were able to replicate and meta-analyse the findings by means of an independent population. Information on insulin treatment provided an important intermediate phenotype for the interpretation of our findings and the understanding of pathophysiological mechanisms. To our knowledge, this is the first study that shows an interaction between *APOC3* variants and BMI to have an effect on type 2 diabetes risk.

Our results show that the effect of variation in the *APOC3* gene is context-dependent. Our findings are not in

Table 4 Odds ratios for insulin treatment in lean and overweight participants with diabetes in RS1

Polymorphism per BMI	Genotype	OR[a]	95% CI	*p* value for trend
BMI ≤26 kg/m^2 [b]				
−482C>T	CC	Reference		
	CT	1.49	(0.89–2.49)	
	TT	1.66	(0.68–4.00)	0.11
−455T>C	TT	Reference		
	TC	1.71	(0.95–3.08)	
	CC	1.64	(0.74–3.62)	0.13
BMI >26 kg/m^2[c]				
−482C>T	CC	Reference		
	CT	0.94	(0.63–1.41)	
	TT	1.26	(0.53–3.03)	0.92
−455T>C	TT	Reference		
	TC	0.83	(0.56–1.25)	
	CC	0.78	(0.40–1.55)	0.34

[a] Adjusted for year of birth and sex

[b] Insulin-treated n=83, non-insulin-treated n=344

[c] Insulin-treated n=131, non-insulin-treated n=575

line with the thrifty genotype hypothesis [27] or with the Barker hypothesis [28]. *APOC3* variants were not associated with BMI. The common *APOC3* variants have an intricate relationship with type 2 diabetes. We hypothesise that lean type 2 diabetes has a distinct molecular basis of its own or that it shares part of its aetiology with type 1 diabetes.

Previous studies Hokanson and colleagues found the *APOC3* promoter variants to be associated with susceptibility to type 1 diabetes [14]. Our findings in the lean type 2 diabetes group are consistent with this finding, with ORs of similar magnitude and direction. Lean type 2 diabetes and type 1 diabetes may both have insulin deficiency as the main characteristic. A partly shared aetiology or at least genetic overlap in disease susceptibility may also explain the increased frequency of lean type 2 diabetes in families with type 1 diabetes and vice versa [12, 13]. Patients with type 2 diabetes who have relatives with type 1 diabetes are leaner and have lower C-peptide concentrations than those with a family history of type 2 diabetes [29].

Our finding that lean carriers of the minor alleles may require insulin therapy more frequently points towards an effect of *APOC3* variants on beta cell function. Nevertheless, the disease process could also involve insulin resistance. The EARS II study reported larger AUCs for glucose and insulin in carriers of the −482T allele after an OGTT [24]. The population of this study consisted of young, healthy, lean offspring of men with premature cardiovascular disease. It would follow therefore that *APOC3* promoter variation increases insulin resistance at a young age, possibly resulting in type 2 diabetes and an earlier need for insulin therapy. Nevertheless, caution should be exercised when extrapolating differences in insulin and glucose AUCs in young healthy participants to relevance for diabetes risk at an older age. In a study of middle-aged participants, male homozygotes of the variant promoter alleles showed less increase in insulin levels after an OGTT [26]. This is in line with our findings in lean participants.

Pathophysiological hypotheses Strikingly, we found an opposite effect of *APOC3* promoter variation in overweight participants, in whom it would seem to protect against type 2 diabetes. Possibly competing risks overruled the effect of the *APOC3* polymorphism and even resulted in an inverse association in overweight participants. Alternatively, there could be a pathophysiological explanation based on the metabolic differences between lean and overweight patients. In lean participants, our findings could be explained as follows. The presence of the promoter polymorphisms results in insulin resistance at a molecular level; thus the insulin-resistant *APOC3* promoter shows impaired insulin-mediated downregulation [19, 20]. Increased ApoC-III plasma levels have been described in type 2 diabetes, but were mostly interpreted as a consequence of the disease [30, 31]. A direct toxic effect of ApoC-III on beta cells was found in in vitro studies by Juntti-Berggren et al. [18]. Indirect mechanisms involving lipoprotein metabolism might play a role, too. However, we did not find an association of the promoter variation with fasting triacylglycerol levels. This, however, does not exclude an effect of the polymorphisms on NEFA flux. Defective inhibition of LPL by ApoC-III might raise levels of circulating NEFAs and thus affect insulin sensitivity and beta cell function [17, 32, 33].

In overweight participants, hyperinsulinaemia may partly restore the insulin-mediated downregulation and may prevent beta cell toxicity. Nonetheless we do not have a clear explanation for a protective effect. A number of studies have shown that LPL metabolism may differ between lean and obese participants. However, it is unknown how differences in lipoprotein composition [34] or post-translational regulation of LPL [35–37] influence susceptibility to type 2 diabetes. Taken together, *APOC3* promoter variation may directly affect beta cell function in lean participants and reduce type 2 diabetes risk in overweight participants by mechanisms that are at present unknown. Alternatively, it may affect type 2 diabetes risk in lean and obese individuals in opposing ways and by mechanisms that involve LPL function.

Study limitations Some limitations of our study need to be considered. Unfortunately, we could not compare our findings with currently published genome-wide association studies, since they were not publicly available for lean and overweight participants separately. We also cannot exclude the possibility that the observed effects are due to linkage disequilibrium with other variants in the *APOC3* gene or other nearby genes in the *APOA1–APOC3–APOA4–APOA5* cluster. Nonetheless, the localisation in an IRE, their defective insulin-mediated downregulation in vitro and the findings by Hokanson and colleagues in type 1 diabetes [14] make these polymorphisms likely candidates for type 2 diabetes susceptibility in lean participants. Another limitation of the study is the relatively small group of participants in which we found a borderline significant interaction for insulin use. Although these results can help focus hypotheses on the mechanism by which *APOC3* polymorphisms affect type 2 diabetes risk, a type 1 error cannot be excluded. These results are merely an encouragement for further research replication in independent cohorts.

Conclusion Our findings indicate that *APOC3* promoter variants significantly interact with BMI at a population-based level, increasing type 2 diabetes risk in lean and

possibly decreasing type 2 diabetes risk in overweight patients. The borderline interaction of the promoter variants with need for insulin treatment suggests beta cell function involvement in lean participants. Our results suggest a genetic overlap between type 1 and lean type 2 diabetes. A subset of type 2 diabetes has already been identified for patients with auto-antibodies, i.e. type 1.5 diabetes or Latent autoimmune diabetes of adulthood [38]. It would seem unlikely that ApoC-III is related to autoimmunity. Our findings may therefore relate to a different subgroup of lean diabetes patients that shows genetic overlap with type 1 diabetes.

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

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