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Interplay between intra-pancreatic fat deposition, exchangeable apolipoproteins, and lipoprotein subclasses

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ABSTRACT

Background and aims: Exchangeable apolipoproteins, including apolipoprotein C-II (apo C-II), apolipoprotein C-III (apo C-III), and apolipoprotein E (apo E), play central roles in the modulation of cardiovascular disease (CVD) risk by readily transferring between anti-atherogenic high-density lipoprotein (HDL) and pro-atherogenic triglyceride-rich lipoproteins (TRL). High intra-pancreatic fat deposition (IPFD) has also emerged as a novel risk factor for CVD. This study aimed to investigate the associations of apo C-II, apo C-III, and apo E with IPFD, as well as with TRL and HDL subclasses.

Methods and results: Abdominal magnetic resonance imaging at 3.0 T was used to quantify IPFD. Plasma levels of apo C-II, apo C-III, and apo E were measured. TRL and HDL subclasses were analysed, with TRL categorised into very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) subclasses (IDL-C, IDL-B, and IDL-A), and HDL into HDL-large, HDL-intermediate, and HDL-small subclasses. Univariate and multivariate linear regression analyses were performed to assess these associations. A total of 128 individuals were analysed. IPFD showed a significant inverse association with both apo C-II and apo C-III, consistent across all statistical models. In the most adjusted model, each unit increase in IPFD was associated with a 0.36-unit decrease in apo C-II ($p = 0.001$) and a 0.31-unit decrease in apo C-III ($p = 0.004$). Furthermore, apo C-II and apo C-III were significantly and inversely associated with all IDL subclasses ($p < 0.02$), but not with VLDL, across all models. No statistically significant association between apo E and IPFD or any IDL subclass was observed in the most adjusted model.

Conclusion: Apo C-II and apo C-III, but not apo E, contribute to the previously observed positive relationship between IPFD and IDL.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, responsible for more than 20 million deaths annually [1]. Among all risk factors of CVD, unfavourable lipid profile (characterised in part by elevated triglyceride-rich lipoproteins (TRL) and low levels of high-density lipoprotein (HDL) cholesterol) may account for up to 55 % of age and sex-independent CVD risk [2,3]. TRL are a group of large, buoyant lipoproteins that primarily transport triglycerides and include very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and their remnants in the fasting state [4]. Due to their high triglyceride content (up to 70 % by weight) [5], TRL are widely recognised for their pro-atherogenic properties. A recent study involving over 90,000 individuals showed a more than two-fold higher risk of CVD in individuals with elevated TRL compared with healthy controls [6]. Genetic evidence further supports a causal role of TRL in CVD, showing that each unit increase in TRL is associated with a 2.6-fold higher risk of CVD [7]. Conversely, HDL cholesterol, known for its cardioprotective effects, has long been established as an independent predictor of both CVD risk and all-risk mortality [8]. Specifically, each unit decrease in HDL cholesterol is associated with a 13 % increase in CVD risk [9]. Raising HDL cholesterol is recommended by major clinical guidelines as

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a part of secondary prevention strategies for CVD [10].

High intra-pancreatic fat deposition (IPFD) has been linked to a wide spectrum of CVD manifestations [11] and dyslipidaemia [12]. Several large-scale cross-sectional studies [12–14] and meta-analysis [15] have consistently demonstrated a significant association of fat in the pancreas with elevated TRL and reduced HDL cholesterol. Recent advancements in testing technologies have enabled the investigation of directly measured—rather than formula-estimated—lipoproteins and their subclasses in relation to IPFD. A novel body of work has recently provided compelling evidence supporting a significant positive association between IPFD and IDL, which is proposed to have greater atherogenic properties than VLDL [16]. In addition, a significant inverse association has been reported between pancreatic fat and large HDL subclasses, which are known to possess markedly greater cardiovascular-protective properties [17]. However, the underlying mechanisms driving these observed associations remain unclear. Exchangeable apolipoproteins, such as apolipoprotein C-II (apo C-II), apolipoprotein C-III (apo C-III), and apolipoprotein E (apo E), play key roles by transferring between TRL and HDL, and are important in the clearance of TRL [19]. Both apo C-II and apo C-III readily transfer between the TRL and HDL pools [18,20], yet they exert opposite functions. Apo C-II promotes the activity of lipoprotein lipase (LPL) by facilitating the access of triglycerides to the enzyme's active site [21]. In contrast, apo C-III impairs lipolysis by restricting LPL's access to its triglyceride substrates and also exhibits a wide range of LPL-independent effects [22,23]. Apo E is also associated with HDL, which serves as a reservoir for apo E redistribution to TRL [24]. The apo E–HDL complex further interacts with TRL to facilitate their hepatic clearance [24]. While there is growing interest in understanding the role of these apolipoproteins in atherogenic lipid profiles, no study to date has explored their role in the context of IPFD.

This study was designed to address the above gaps by first examining the relationships of apo C-II, apo C-III, and apo E with IPFD, and then assessing the role of these apolipoproteins in the previously observed associations of IPFD with TRL and HDL subclasses.

2. Methods

2.1. Study design and participants

This cross-sectional study was conducted as part of the COSMOS programme and involved adults who underwent magnetic resonance imaging (MRI) of the pancreas for the purpose of research. The study was approved by the Health and Disability Ethics Committee of New Zealand (13/STH/182) and was conducted adhering to the principles of the Declaration of Helsinki. The study included a multiethnic cohort of adults of both sexes who resided in Auckland (New Zealand) at the time of the study. Participants were excluded if they had a history of type 1 or gestational diabetes, autoimmune diseases, liver disease, malignancy, pregnancy, breastfeeding, or cognitive disabilities. Exclusion criteria also included a history of pancreatic disorders, including autoimmune pancreatitis, hereditary pancreatitis, chronic pancreatitis, pancreatic lipoma, congenital abnormalities of the pancreas, post-endoscopic retrograde cholangiopancreatography pancreatitis, pancreatic trauma, prior surgical or endoscopic interventions involving the pancreas, or cystic fibrosis. Additionally, individuals with contraindications for MRI, including the presence of metallic foreign bodies, pacemakers, or other implanted electronic devices, or severe chronic obstructive pulmonary disease that impaired breath-holding, were excluded.

2.2. Imaging protocol and intra-pancreatic fat quantification

All participants underwent abdominal MRI using a 3.0 T MAGNETOM scanner (Siemens Healthineers, Erlangen, Germany) at the Centre for Advanced MRI, University of Auckland, following a standardised imaging protocol. The detailed imaging protocol has been outlined elsewhere [25]. In-phase, out-of-phase, fat-only, and water-only images were acquired and exported for further analysis.

For the quantification of IPFD, a modified 'MR-opsy' technique was adopted [25]. In brief, two 5-mm-thick candidate slices of the pancreas were selected from the out-of-phase images using MicroDicom software (MicroDicom, Sofia, Bulgaria). Three regions of interest (ROIs) were then placed on the head, body, and tail of the pancreas using ImageJ software (National Institutes of Health, Bethesda, MD). To avoid the inclusion of non-parenchymal tissues—such as blood vessels and peripancreatic fat—a threshold range of 1–20 % was applied to these ROIs. The fat fraction was calculated as the signal from fat protons divided by the total signal from both fat and water protons, in accordance with previously published methods [55]. IPFD quantification was performed by two independent assessors, each of whom measured IPFD from two candidate slices. The results were then averaged to obtain a final value.

2.3. Laboratory measurements

Venous blood samples were collected in EDTA and lithium heparin tubes following an overnight fast of 8–10 h. Freshly collected, never-frozen blood samples were sent to LabPlus, an accredited tertiary laboratory located at the Auckland City Hospital, New Zealand, for the analyses of total cholesterol (mg/dL), triglycerides (mg/dL), HDL cholesterol (mg/dL), fasting plasma glucose (mmol/L), and haemoglobin A1c (HbA1c, mmol/mol). Hypertriglyceridaemia was defined as triglyceride levels $\geq$150 mg/dL, in accordance with established guidelines [27]. Levels of apo C-II, apo C-III, and apo E were measured using the MILLIPLEX ® MAP Human Apolipoprotein Magnetic Bead Panel (Cat # HAP0-8062; Millipore, USA) [28]. The intra- and inter-assay coefficients of variation for all were $<$10 % and $<$20 %, respectively.

2.4. Lipoprotein analyses

For the assessment of TRL and HDL subclasses, fasting blood samples were collected in EDTA tubes, centrifuged at 4000 g at 4 °C for 5 min, and the resulting plasma was aliquoted and stored at −80 °C until batch analysis. Lipoprotein subclasses analyses were performed using the Lipoprint System (Quantimetrix Corp., Redondo Beach, CA, USA) according to the manufacturer's protocols. In brief, plasma samples were thawed at room temperature prior to analysis. For TRL subclasses, 25 μL of plasma was loaded onto low-density lipoprotein (LDL)-specific precast linear polyacrylamide gel tubes, followed by the addition of 200 μL of loading gel [29]. For HDL subclasses, 25 μL of serum was loaded onto HDL-specific gel tubes with 300 μL of loading gel [17,30]. The loaded tubes were sealed with parafilm and gently inverted to mix the sample with the loading gel solution. All gel tubes were photo-polymerised for 30 min at room temperature, followed by electrophoresis at 500V and 3 mA per tube in the provided buffers (Tris-hydroxymethyl aminomethane: 66.1 g/100 g; boric acid: 33.9 g/100 g; pH 8.2–8.6) for 60 min (for TRL subclasses) and 50 min (for HDL subclasses), respectively. Quality controls were performed using Liposure Human Serum Lipoprotein Control (Quantimetrix Corp., Redondo Beach, CA, USA). Following electrophoresis, the gel tubes were allowed to rest at room temperature for 30 min and then scanned using an ArtixScan M1 digital scanner (Microtek International Inc., Santa Fe Springs, CA, USA). Due to the sieving effect of the gel matrix, lipoproteins and their subclasses were separated into distinct stained bands based on their relative electrophoretic mobility (Rf). A TRL subclasses profile of decreasing size and increasing density with one VLDL band and 3 IDL bands was obtained from the LDL-specific gel tubes [16]. Similarly, ten HDL fractions (HDL-1 to HDL-10), grouped into three subclasses - HDL-large (HDL-1 to 3), HDL-intermediate (HDL-4 to 7), and HDL-small (HDL-8 to 10), were identified using HDL-specific gel tubes [17]. The proportion of each TRL and HDL subclass was expressed as the percentage of the area under the curve (AUC%). Absolute concentrations (mg/dL) were then calculated by multiplying the AUC% by total cholesterol (for TRL subclasses) or by total HDL cholesterol (for HDL subclasses), respectively.

2.5. Other covariates

Demographic characteristics, including age, ethnicity, and sex, were collected from all participants using a standardised form. Anthropometric measurements—weight (kg), height (cm), waist circumference (cm), and hip circumference (cm)—were obtained in duplicate following a standardised protocol and subsequently averaged. The waist-to-hip ratio was calculated by dividing waist circumference by hip circumference.

2.6. Statistical analysis

Statistical analyses were conducted using Prism software version 9 (GraphPad) and IBM SPSS Statistics version 29.0.1.0 for Macintosh (IBM Corp., Armonk, NY, USA). Less than 5 % of the data across all measurements were missing completely at random and were imputed using the last observation carried forward method [31] and the multiple imputation method [32]. A fully conditional specification approach using regression-based methods was applied to generate five imputed datasets, with a maximum of 100 case draws per variable [33]. The variables included in the imputation process were age, sex, ethnicity, weight, height, IPFD, waist circumference, hip circumference, HbA1c, triglycerides, total cholesterol, HDL cholesterol, and fasting plasma glucose. The Shapiro-Wilk test was used to assess data normality. Continuous variables with a normal distribution were presented as mean (standard error of the mean [SEM]), while non-normally distributed variables were reported as median (interquartile range). Variables with skewed distributions were logarithmically transformed prior to analysis. Univariate and multivariate linear regression analyses were performed to explore associations between continuous variables of interest. Three statistical models were constructed: an unadjusted model (model 1); a model adjusted for age, sex, and ethnicity (model 2); and the most adjusted model (model 3) including age, sex, ethnicity, waist-to-hip ratio, fasting plasma glucose, total cholesterol, and presence or absence of hypertriglyceridaemia. Results are presented as β coefficients and p-values. A two-tailed p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Study cohort characteristics

A total of 128 individuals met the eligibility criteria and were included in the analysis. Among them, 50 (39.06 %) identified as New Zealand European, 27 (21.09 %) as Asian, 27 (21.09 %) as other ethnicities, 21 (16.41 %) as Māori, and 3 (2.34 %) as Pacific Islander. Out of the 128 individuals, 35 (27.34 %) had hypertriglyceridaemia whereas 93 (72.66 %) had normal levels of triglycerides. Other characteristics of the study cohort are presented in Table 1.

Table 1
Participant characteristics.

Characteristic	Overall (n = 128)
Age (years)	57.60 (43.56, 67.29)
Sex (%)	
Men	n = 76 (59.38 %)
Women	n = 52 (40.63 %)
Waist-to-hip ratio	0.96 (0.88, 1.01)
Body mass index (kg/m^2)	27.11 (23.57, 31.12)
IPFD (%)	9.63 (7.61, 10.91)
HbA1c (mmol/mol)	36.97 (35.16, 40.04)
Triglycerides (mg/dL)	111.05 (79.84, 169.02)
Total cholesterol (mg/dL)	177.68 (151.41, 208.51)
HDL cholesterol (mg/dL)	50.30 (41.83, 61.90)

Footnote: Continuous variables are reported as median and interquartile range, and categorical variables are presented as numbers and frequencies. Abbreviations: HDL, high-density lipoprotein; IPFD, intra-pancreatic fat deposition.

3.2. Associations of intra-pancreatic fat deposition with apolipoproteins

Significant associations between IPFD and apo C-II were observed in the unadjusted model, the model adjusted for age, sex, and ethnicity, and the most adjusted model (Fig. 1). Specifically, each unit increase in IPFD was associated with decreases in apo C-II of 0.28 units ($p = 0.001$), 0.29 units ($p = 0.003$), and 0.36 units ($p = 0.001$), respectively (Table 2). Similarly, significant inverse associations between IPFD and apo C-III were observed across all three models, with decreases of 0.25 units ($p = 0.004$), 0.26 units ($p = 0.008$), and 0.31 units ($p = 0.004$) per unit increase in IPFD (Table 2). However, no significant association was found between IPFD and apo E in any of the models (Table 2).

3.3. Associations of apolipoproteins with triglyceride-rich lipoprotein subclasses

No significant association between apo C-II and VLDL was observed in any of the three models. However, apo C-II showed consistent and significant inverse associations with IDL subclasses (IDL-C, IDL-B, and IDL-A) across all models (Table 3). In the fully adjusted model, each unit increase in apo C-II corresponded to decreases of 0.16 units ($p = 0.003$) in IDL-C, 0.27 units ($p = 0.002$) in IDL-B, and 0.29 units ($p < 0.001$) in IDL-A. Similarly, apo C-III was not significantly associated with VLDL but demonstrated consistent and significant inverse associations with all three IDL subclasses. In the most adjusted model, each unit increase in apo C-III was linked to reductions of 0.16 units in IDL-C ($p = 0.002$), 0.29 units in IDL-B ($p < 0.001$), and 0.29 units in IDL-A ($p = 0.001$). For apo E, a significant inverse association with IDL-C was observed in the unadjusted model ($p = 0.037$) and the model adjusted for age, sex, and ethnicity ($p = 0.027$), but this association was no longer significant in the most adjusted model ($p = 0.056$) (Table 3).

3.4. Associations of apolipoproteins with high-density lipoprotein subclasses

No significant associations were observed between apo C-II or apo C-III and any HDL subclasses across all three models (Table 4). In contrast, apo E was significantly and positively associated with the HDL-large subclass, with each unit increase in apo E corresponding to a 0.15-unit increase in HDL-large ($p = 0.044$) (Table 4). Detailed associations between the apolipoproteins and the ten HDL fractions are provided in Supplementary Table 1.

4. Discussion

This is the first study to investigate the relationship between IPFD, assessed using gold-standard 3.0-T MRI, and exchangeable apolipoproteins—apo C-II, apo C-III, and apo E. It advances the field by examining these associations in the context of TRL and HDL metabolism. The primary finding is a significant inverse association between IPFD and both apo C-II and apo C-III (Fig. 2). Secondarily, apo C-II and apo C-III were inversely associated with all IDL subclasses, but not with VLDL. In contrast, apo E showed no association with either IPFD or IDL (Fig. 2). Importantly, these findings were independent of hypertriglyceridaemia, a known modulator of apolipoprotein functions [34–36]. In addition, covariates including demographic characteristics (age, sex, ethnicity), anthropometry (waist-to-hip ratio), markers of glucose metabolism (fasting plasma glucose) and lipid metabolism (total cholesterol) —all known to influence both IPFD and lipid metabolism—were accounted for [13,15,37,38].

For the first time, we observed a significantly inverse association between apo C-II and IPFD, consistently across all three models. Individuals with pathogenic APOC2 variants frequently present with acute pancreatitis [39,40], a condition in which fatty pancreas has been

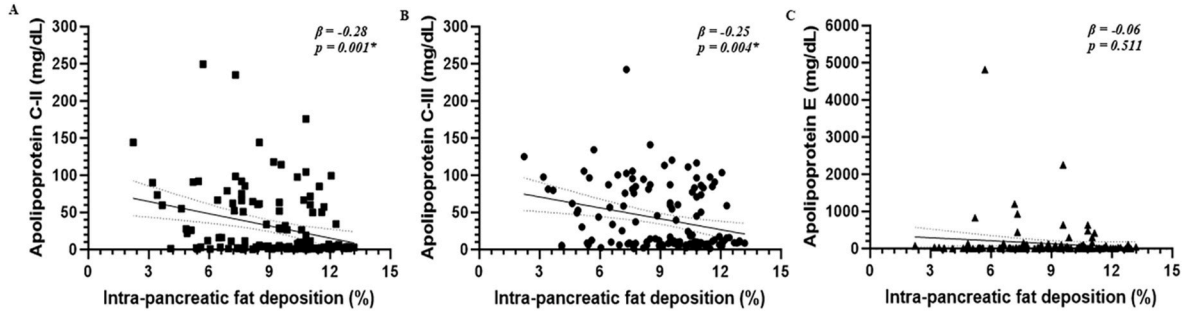

Fig. 1. Associations of intra-pancreatic fat deposition with apolipoprotein C-II, apolipoprotein C-III, and apolipoprotein E. Footnotes: *p* values and β coefficients were derived from unadjusted regression analyses. Apolipoprotein C-II, apolipoprotein C-III, and apolipoprotein E concentrations were measured in mg/dL. Intra-pancreatic fat deposition was expressed in %. The dashed lines represent the 95 % confidence interval.

Table 2
Relationships of intra-pancreatic fat deposition with apolipoproteins.

Dependent variable	Mean ± SEM (mg/dL)	Model 1		Model 2		Model 3	
		β	*p* value	β	*p* value	β	*p* value
Apolipoprotein C-II	8.42 ± 1.17	**−0.28**	**0.001**	**−0.29**	**0.003**	**−0.36**	**0.001**
Apolipoprotein C-III	20.84 ± 1.12	**−0.25**	**0.004**	**−0.26**	**0.008**	**−0.31**	**0.004**
Apolipoprotein E	17.64 ± 1.18	−0.06	0.511	−0.08	0.418	−0.19	0.096

Footnotes: Results are from the univariate and multivariate linear regression analyses in 128 participants. Data are presented as β coefficients and p values. Statistically significant values ($p < 0.05$) are shown in bold. Model 1 was unadjusted; Model 2 was adjusted for age, sex, and ethnicity; Model 3 was adjusted for age, sex, ethnicity, waist-to-hip ratio, fasting plasma glucose, total cholesterol, and hypertriglyceridaemia. Data for intra-pancreatic fat deposition, age, waist-to-hip ratio, fasting plasma glucose, total cholesterol, apolipoprotein C-II, apolipoprotein C-III, and apolipoprotein E were log-transformed.

Table 3
Relationships of apolipoproteins with triglyceride-rich lipoprotein subclasses.

Dependent variables	Model 1		Model 2		Model 3	
	β	*p* value	β	*p* value	β	*p* value
Apolipoprotein C-II						
VLDL	−0.08	0.387	−0.10	0.271	0.003	0.959
IDL-C	**−0.22**	**0.014**	**−0.26**	**0.004**	**−0.16**	**0.003**
IDL-B	**−0.29**	**0.001**	**−0.30**	**< 0.001**	**−0.27**	**0.002**
IDL-A	**−0.32**	**< 0.001**	**−0.33**	**< 0.001**	**−0.29**	**< 0.001**
Apolipoprotein C-III						
VLDL	−0.07	0.459	−0.09	0.324	<-0.01	0.957
IDL-C	**−0.21**	**0.019**	**−0.25**	**0.006**	**−0.16**	**0.002**
IDL-B	**−0.30**	**< 0.001**	**−0.31**	**< 0.001**	**−0.29**	**< 0.001**
IDL-A	**−0.30**	**< 0.001**	**−0.32**	**< 0.001**	**−0.29**	**0.001**
Apolipoprotein E						
VLDL	−0.07	0.419	−0.08	0.394	0.01	0.799
IDL-C	**−0.19**	**0.037**	**−0.20**	**0.027**	−0.10	0.056
IDL-B	−0.06	0.495	−0.07	0.470	−0.03	0.723
IDL-A	−0.17	0.064	−0.17	0.060	−0.12	0.181

Footnotes: Results are from the univariate and multivariate linear regression analyses among 128 participants. Data are presented as β coefficients and p values. Statistically significant values ($p < 0.05$) are shown in bold. Model 1 was unadjusted; Model 2 was adjusted for age, sex, and ethnicity; Model 3 was adjusted for age, sex, ethnicity, waist-to-hip ratio, fasting plasma glucose, total cholesterol, and triglyceridaemia. Data for intra-pancreatic fat deposition, age, waist-to-hip ratio, fasting plasma glucose, total cholesterol, apolipoprotein C-II, apolipoprotein C-III, apolipoprotein E, VLDL, IDL-C to IDL-A were log-transformed.
Abbreviations: IDL, intermediate-density lipoprotein; VLDL, very low-density lipoprotein.

Table 4
Relationships of apolipoproteins with high-density lipoprotein subclasses.

Dependent variables	Model 1		Model 2		Model 3	
	β	*p* value	β	*p* value	β	*p* value
Apolipoprotein C-II						
HDL-large	0.02	0.837	−0.05	0.539	−0.02	0.787
HDL-intermediate	0.02	0.807	−0.05	0.548	0.02	0.783
HDL-small	−0.06	0.491	−0.07	0.434	−0.03	0.756
Apolipoprotein C-III						
HDL-large	<-0.01	0.986	−0.08	0.326	−0.06	0.453
HDL-intermediate	0.05	0.573	−0.03	0.729	0.03	0.663
HDL-small	−0.02	0.840	−0.02	0.791	0.01	0.895
Apolipoprotein E						
HDL-large	0.10	0.267	0.07	0.436	**0.15**	**0.044**
HDL-intermediate	0.05	0.562	0.02	0.782	0.13	0.051
HDL-small	−0.04	0.663	−0.04	0.668	0.02	0.829

Footnotes: Results are from the univariate and multivariate linear regression analyses in 128 participants. Data are presented as β coefficients and p values. Statistically significant values ($p < 0.05$) are shown in bold. Model 1 was unadjusted; Model 2 was adjusted for age, sex, and ethnicity; Model 3 was adjusted for age, sex, ethnicity, waist-to-hip ratio, fasting plasma glucose, total cholesterol, and hypertriglyceridaemia. Data for intra-pancreatic fat deposition, age, waist-to-hip ratio, fasting plasma glucose, total cholesterol, apolipoprotein C-II, apolipoprotein C-III, apolipoprotein E, and HDL-large subclass were log-transformed.
Abbreviation: HDL, high-density lipoprotein.

established as an underlying driver [41]. Additionally, the APOC2 loss-of-function animal model demonstrated vascular accumulation of lipids and lipid-laden macrophages, as well as ectopic fat accumulation, despite being maintained on a normal diet [42]. In parallel, we also identified a significantly inverse association between apo C-II and IDL.

Apo C-II plays an essential regulatory role in triglyceride metabolism and the clearance of TRL [43]. Previous studies in animal models homozygous for the APOC2 mutation demonstrated a sevenfold increase in the proportion of incompletely lipolysed TRL compared with wild-type controls [44]. Similarly, individuals with genetic apo C-II deficiency typically exhibit impaired hydrolysis of triglyceride-rich lipoproteins, resulting in hypertriglyceridaemia and an increased risk of CVD [18]. Supporting this, a pharmacological study showed that an apo C-II

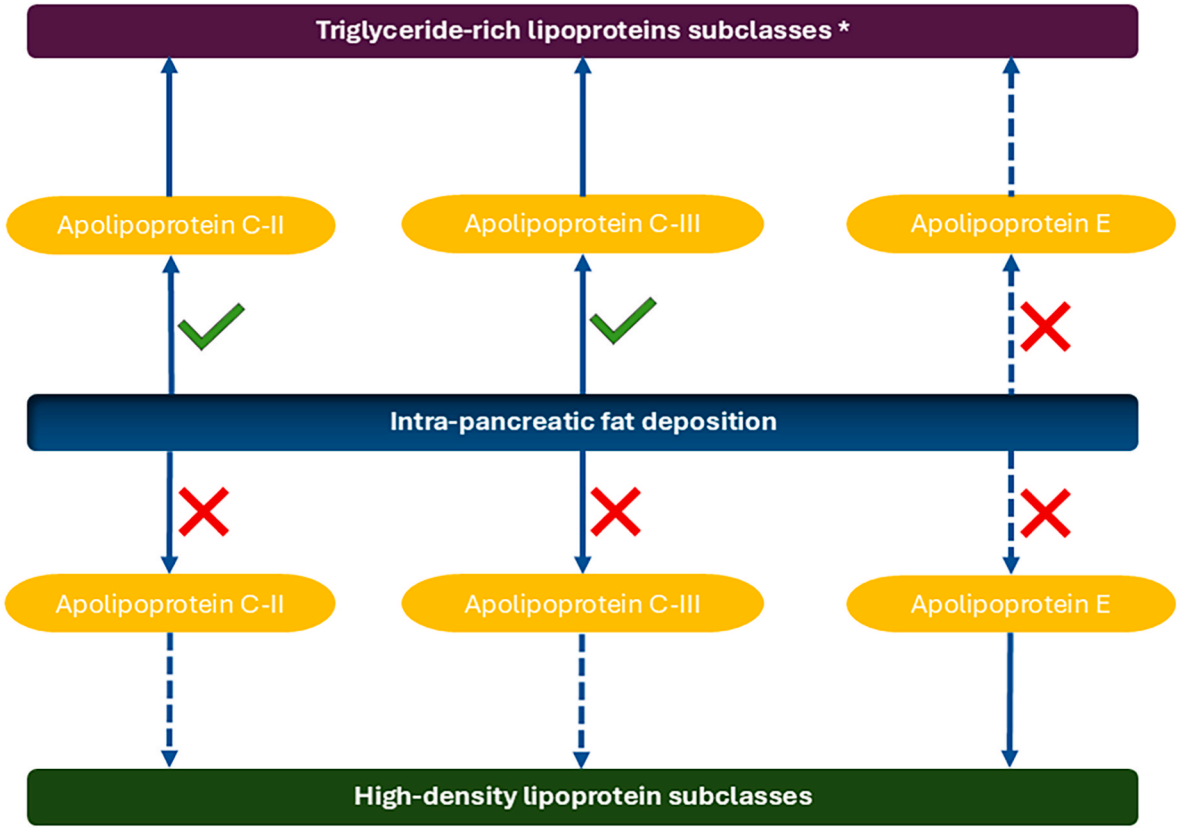

Fig. 2. Summary of key findings. Footnotes: Solid lines indicate statistically significant associations, while dashed lines represent non-significant associations between parameters. Green check marks (✔) denote apolipoproteins that explain the previously observed associations between IPFD and specific lipoprotein subclasses. Red crosses (✖) indicate apolipoproteins that do not explain these associations. * In this figure, triglyceride-rich lipoproteins refer specifically to intermediate-density lipoproteins. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

mimetic peptide effectively ameliorated hypertriglyceridemia characterised by a predominance of intermediate remnant-like particles [45]. Furthermore, D6PV, a dual apo C-II mimetic and apo C-III antagonist, has demonstrated marked potential by lowering triglyceride levels by nearly 80 % [46]. Consequently, the inverse associations of apo C-II with both IDL and IPFD indirectly support the notion that apo C-II, at least in part, contributes to the previously observed positive relationship between IPFD and atherogenic IDL [16].

In addition, our study is the first to examine the association between apo C-III and IPFD in a non-interventional, cross-sectional context. We found a significant inverse association between apo C-III and IPFD. However, this finding differs somewhat from a 2025 randomised controlled trial, which reported a positive correlation between changes in fasting apo C-III and changes in IPFD following an 8-week dietary intervention [47]. This discrepancy is likely attributable to differences in study design and population characteristics. While the previous randomised controlled trial assessed temporal changes in apo C-III levels in individuals with type 2 diabetes following an intervention, our cross-sectional study focused on steady-state physiology within a broader cohort representative of the general population, including both normoglycaemic and dysglycaemic individuals. In parallel, we also found an inverse association between apo C-III and IDL, but not with VLDL. This is consistent with a previous report of significantly lower apo C-III in IDL among individuals with dysglycaemia [48]. While apo C-III is traditionally regarded as an inhibitor of LPL that reduces the conversion of TRL to LDL, it also exerts a wide range of LPL-independent actions [23]. Notably, these include interactions with hepatic lipoprotein receptors such as heparan sulphate proteoglycan (HSPG), LDL receptors (LDLR), and LDL receptor-related protein 1 (LRP1) [49–51]. Human kinetic studies support the role of apo C-III in modulating hepatic remnant uptake without directly influencing LPL-mediated lipolysis of large TRL particles [51,52]. Individuals with null mutations in the APOC3 gene also do not show altered direct removal of VLDL [53], but instead demonstrate preferential hepatic clearance of smaller TRL particles such as IDL [20,52]. Taken together, we provided a mechanistic explanation for the previously observed positive association between IPFD and IDL (but not VLDL), suggesting that reduced apo C-III levels associated with high IPFD may, at least in part, contribute to impaired hepatic clearance of smaller, rather than larger, TRL particles.

The limitations of the present study should be acknowledged. First, due to its cross-sectional design, causality cannot be inferred; randomised controlled trials specifically designed for this purpose are warranted. Second, as only fasting blood samples were analysed, the role of chylomicrons was not evaluated. Further research is needed to explore the relationships among these apolipoproteins, IPFD, and chylomicrons. Third, lifestyle factors such as alcohol consumption and tobacco smoking, which can influence apolipoprotein levels, were not adjusted for in this study [54]. Future research should consider including these variables in their analyses.

5. Conclusion

This study is the first to highlight the roles of apo C-II and apo C-III in explaining the previously observed association between IPFD and atherogenic TRL (specifically IDL). These novel findings suggest that IPFD may contribute to CVD risk through disturbances in TRL metabolism, providing new insights into the emerging understanding of IPFD and its implications for cardiometabolic health.

Author contributions

MSP: conceptualisation; YL: formal analysis; WK, YL, XS and LSH: participant recruitment and data acquisition; YL: writing—original draft preparation; IRS, LSH, WK, XS, and MSP: review and editing; MSP: funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2025.104280

Data availability

Some or all datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

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