Received: 7 August 2024 | Revised: 4 February 2025 | Accepted: 7 February 2025

DOI: 10.1111/obr.13914

REVIEW

OBESITY Reviews WILEY

Relationship of fat in the pancreas with cardiovascular disease: A systematic review and meta-analysis

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Summary

Background: General adiposity is a well-known risk factor for cardiovascular disease. By contrast, the interconnection between high intra-pancreatic fat deposition and cardiovascular disease has been scantily investigated. This field-wide systematic review aimed to map the available evidence on cardiovascular disease according to the fat content of the pancreas.

Methods: A literature search using two electronic databases (MEDLINE and Embase) was conducted independently by two reviewers. Studies reporting on the association between intra-pancreatic fat deposition and cardiovascular disease in humans were included. Where meta-analysis was possible, data were pooled using a random-effects method.

Results: A total of 16 studies published between 1966 and 2024 were included. The most credible findings across domains of heart diseases, diseases of arteries, arterioles, and capillaries, as well as subclinical atherosclerosis provided supportive evidence of a positive relationship between high intra-pancreatic fat deposition and cardiovascular disease. Meta-analysis showed that high intra-pancreatic fat deposition was significantly associated with increased aortic intima-media thickness (mean difference: 0.19 mm; 95% confidence interval: 0.12–0.26; $p < 0.001$), increased carotid intima-media thickness (mean difference: 0.06 mm; 95% confidence interval: 0.03–0.08; $p < 0.001$), and increased vascular stiffness (mean difference: 167 cm/s; 95% confidence interval: 81–254; $p < 0.001$).

Conclusion: The accumulated evidence from more than 7000 people demonstrates a tangible connection of intra-pancreatic fat deposition with cardiovascular disease (especially, subclinical atherosclerosis). Purposely designed investigations of high intra-pancreatic fat deposition as an additional risk factor (independent of general adiposity) for cardiovascular disease are warranted.

KEYWORDS
atherosclerosis, cardiovascular disease, intra-pancreatic fat deposition, fatty pancreas

1 | INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death worldwide.[1] In 2019, approximately 17.9 million people died from CVD – responsible for 32% of worldwide deaths.[1] Many risk factors contribute to CVD, the most common being diabetes, general adiposity, hypertension, and hyperlipidemia.[2] The high prevalence of these risk factors explains the substantial global burden of CVD. Consequently, many predictive scores are used in clinical settings to assess risk for CVD, helping reduce the burden of CVD at individual level.[3]

However, current predictive scores using conventional risk factors for CVD do not accurately predict all individuals at risk for CVD.[4] It is a pressing research priority to identify missing risk factors for the residual population, enabling the development of better preventative and therapeutic interventions. While the link between general adiposity and increased CVD risk is well established,[5] the potential role of high intra-pancreatic fat deposition (IPFD) has received limited attention.[6] IPFD (measured on a continuous scale) is defined as the diffuse presence of fat in the pancreas in both health and disease states.[6] A small amount of IPFD is a constituent of the normal human pancreas. Fatty change of the pancreas refers to disorder characterized by excess IPFD.[6] Fatty change of the pancreas is the most common pathology of the pancreas (with a conservatively estimated prevalence of around 20% in general populations) and many individuals develop it independent of general adiposity.[7] While some clinical studies have found a significant relationship between fat in the pancreas and CVD and others have not, the association between IPFD and CVD has yet to be assessed systematically. Gaining deeper insights into the relationship between IPFD and CVD could enhance risk assessment strategies and contribute to more effective prevention and management of CVD.

The aim was to systematically review clinical studies that investigated the relationship between fat in the pancreas and CVD.

2 | MATERIALS AND METHODS

This systematic review was conducted according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[8]

2.1 | Search strategy

The search strategy was designed with the assistance of an experienced subject librarian. Two reviewers (Y.Z. and Y.L.) independently searched the electronic databases MEDLINE and Embase until October 1st, 2024. The search strings are presented in Supporting Information. The initial screening of publications was based on title and abstract. Full-text articles of potentially relevant publications were retrieved and examined for eligibility. Reference lists of retrieved full-text articles and personal libraries were also reviewed to identify additional relevant publications.

2.2 | Eligibility criteria

Two authors (Y.Z. and Y.L.) assessed the eligibility of studies, and any disagreement was resolved by discussion with the senior author (M.S.P.). Studies reporting on the association of IPFD with objectively measured and clinically meaningful CVD outcomes were eligible. Given that the relationship of fat in the pancreas with diabetes and metabolic syndrome was previously investigated in at least two systematic reviews,[9,10] primary studies that reported on diabetes (i.e., without investigation of its microvascular or macrovascular complications), arterial hypertension, general or abdominal adiposity, or dyslipidemia alone (i.e., without reporting on CVD) as outcomes were beyond the scope of the present systematic review. Only studies that determined IPFD with the use of modern imaging techniques (magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), computed tomography (CT), ultrasound (US), endoscopic ultrasound (EUS)), or post-mortem examination were considered. Studies that investigated peripancreatic or visceral fat (and not reported on IPFD separately) were not considered. The presence of CVD was taken as reported in primary studies and grouped, in line with the International Classification of Diseases version 10 (ICD-10), into the domains of heart diseases (e.g., ischemic heart disease [IHD], acute myocardial infarction, cardiac complications); diseases of arteries, arterioles, and capillaries (e.g., atherosclerosis, vessel calcifications, atherosclerotic retinopathy); and subclinical atherosclerosis (determined based on intima-media thickness of vessels, carotid plaque, or vascular stiffness). Studies that reported only on cardiac MRI or echocardiographic parameters were excluded. Editorials, reviews, conference proceedings, animal studies, and case reports or case series (involving less than 10 participants) were also excluded. Besides, studies were excluded if they determined IPFD based on association with genetic variants, used laboratory markers alone, and did not involve both sexes.

2.3 | Data extraction

The following data were collected from each primary study, if available: study characteristics (year published, country of study, study population); characteristics of individuals (total number, proportion of women, age, BMI, proportion of individuals with fatty change of the pancreas); method of IPFD determination (MRI, CT, EUS, US, post-mortem examination); ascertainment of IPFD; method of CVD determination (ICD-10, pulse wave velocity [PWV], CT, MRI, US), positron emission tomography (PET), post-mortem examination); CVD outcomes.

2.4 | Methodological quality

Two authors (Y.Z. and Y.L.) assessed the methodological quality of the included studies using a tool designed and validated for prevalence

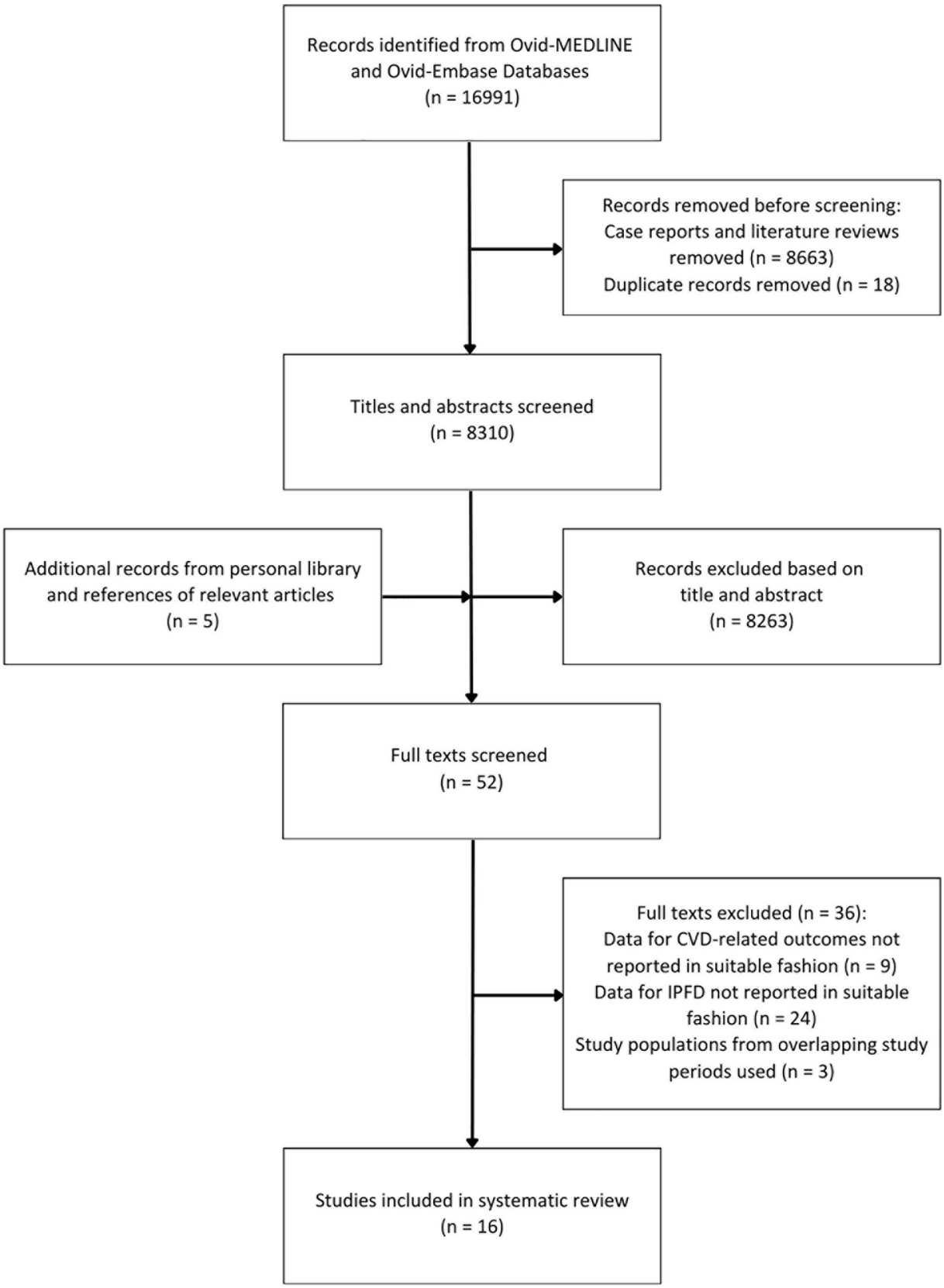

FIGURE 1 Flowchart of the study selection process. Abbreviations: CVD, cardiovascular disease; IPFD, intra-pancreatic fat deposition.

TABLE 1 Baseline characteristics of the included studies.

Study	Year	Country	Study design	Study population	Total number of individuals, n	Women, n (%)	Age, years	BMI, kg/m^2
Chan et al[13]	2022	China	Cohort	Individuals from general population	631	388 (61)	48 (11) [a]	22.6 (3.5) [a]
Hannukainen et al[14]	2016	Finland	Cross-sectional	Individuals referred to CAD screening	30	15 (50)	63 (3) [a, b]	28.6 (1) [a, b]
Jeong et al[15]	2018	South Korea	Cross-sectional	Individuals with T2DM	186	107 (57)	58 (15) [a]	25.9 (4.1) [a]
Kim et al[16]	2014	South Korea	Cross-sectional	Individuals with T2DM	198	114 (58)	59 (15) [a]	25.9 (4.1) [a]
Koo et al[17]	2020	USA	Cross-sectional	Individuals from general population	3951	1752 (44)	57 (11) [a, b]	27 (24–30) [b, e]
Kul et al[18]	2019	Turkey	Cross-sectional	Individuals from general population	103	65 (63)	52 (10) [a, b]	33.1 (5.3) [a, b]
Li et al[19]	2024	China	Cross-sectional	Individuals referred to weight management programme	128	69 (54)	33 (8) [a, b]	32.7 (4.6) [a, b]
Meloni et al[20]	2023	Italy	Cross-sectional	Individuals with thalassemia major	308	182 (59)	40 (32–45) [c]	22.3 (20.2–24.6) [e]
Ordulj et al[21]	2023	Croatia	Cross-sectional	Individuals who underwent urgent CT scan upon hospital admission	302	85 (28)	53 (32–64) [c]	NR
Ozturk et al[22]	2018	Turkey	Cross-sectional	Individuals with MASLD and healthy volunteers	138	7 (5)	34 (7) [a, b]	29.5 (3.2) [a, b]
Sahin et al[23]	2023	Turkey	Cross-sectional	Individuals with acute coronary syndrome	99	25 (25)	61 (10) [a, b]	26.7 (3.2) [a, b]
Sahin and Karadeniz[24]	2022	Turkey	Cross-sectional	Individuals with MASLD	183	106 (58)	51 (9) [a, b]	29.9 (4.3) [a, b]
Sotoudehmanesh et al[25]	2019	Iran	Cross-sectional	Individuals referred to EUS examination	228	115 (50)	57 (15) [a]	25.7 (4.5) [a]
Stamm[26]	1984	Switzerland	Cross-sectional	Cadavers	112	45 (40)	62 (18–89) [c]	NR
Sun et al[27]	2021	China	Cross-sectional	Individuals with T2DM	337	136 (40)	63 (11) [a, b]	25.7 (3.1) [a, b]
Walters[28]	1966	Australia	Cross-sectional	Cadavers	200	75 (37)	13–92 [d]	NR

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CT, computed tomography; EUS, endoscopic ultrasound; IPFD, intra-pancreatic fat deposition; MASLD, metabolic dysfunction-associated steatotic liver disease; NR, not reported; T2DM, type 2 diabetes mellitus.

[a]Mean (standard deviation).

[b]Based on the largest subgroup in the study.

[c]Median (range).

[d]Range.

[e]Mean (range).

and incidence studies – the Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross-sectional studies and cohort studies.[11] The checklist for cross-sectional and cohort studies evaluated each study using 8 and 11 questions, respectively, based on the answers of 'yes', 'no', 'unclear', or 'not applicable' to the questions. Any disagreement was resolved by discussion with the senior author (M.S.P.).

2.5 | Statistical analysis

Meta-analysis was conducted if two or more studies reported on the same CVD outcome (as mean and standard deviation) in individuals with versus without fatty change of the pancreas.[12] Studies that investigated a CVD outcome in combination with other diseases were meta-analyzed only if data for individuals with CVD could be reconstructed. Meta-analysis was conducted using RevMan version 5.4 (The Cochrane Collaboration, London, England). The overall effect was assessed using the Z-test. A random-effects model was used to provide the most conservative estimate, and a p-value of < 0.05 was deemed to be statistically significant. Statistical heterogeneity between the studies was assessed using the I^2 test. High statistical heterogeneity was defined as I^2 values greater than 75%, moderate heterogeneity – as 25% to 75%, and low heterogeneity – as less than 25%.

3 | RESULTS

3.1 | Study characteristics

A total of 16,991 publications were retrieved from two databases, and full texts were obtained for 52 publications to apply the eligibility criteria further (Figure 1). Sixteen studies met all the eligibility criteria and were included in the systematic review (Table 1).[13–28] The overall methodological quality of the included studies is presented in Table 2. Fourteen studies used imaging modalities to determine fat in the pancreas (Table 3).[13–25,27] These included four studies that used MRI or MRS,[13,14,19,20] five studies that used CT,[15–17,21,27] four studies that used US,[18,22–24] and one study that used EUS.[25] Two studies determined fat in the pancreas through post-mortem examination.[26,28] Five studies reported on heart diseases,[13,14,20,23,25] five studies reported on diseases of arteries, arterioles, and capillaries,[15,17,21,26,28] and seven studies reported on subclinical CVD.[16,18,19,22,24,25,27]

3.2 | Relationship of fat in the pancreas with heart diseases

Five studies investigated the association of IPFD with IHD or cardiac complications. [13,14,20,23,25] Sotoudehmanesh et al reported that individuals with fatty change of the pancreas, when compared to those

TABLE 2 Methodological quality assessment of the included studies.

Study	JBI appraisal score [a]										
Cohort	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Chan et al[13]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Cross-sectional			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Hannukainen et al[14]			Y	Y	Y	Y	Y	Y	Y	Y	
Jeong et al[15]			Y	Y	Y	Y	Y	Y	Y	Y	
Kim et al[16]			Y	Y	Y	Y	Y	Y	Y	Y	
Koo et al[17]			Y	Y	Y	Y	Y	Y	Y	Y	
Kul et al[18]			Y	Y	Y	Y	Y	Y	Y	Y	
Li et al[19]			Y	Y	Y	Y	Y	Y	Y	Y	
Meloni et al[20]			N	Y	Y	Y	Y	Y	Y	Y	
Ordulj et al[21]			Y	Y	Y	Y	Y	Y	Y	Y	
Ozturk et al[22]			Y	Y	Y	Y	Y	Y	Y	Y	
Sahin et al[23]			Y	Y	Y	Y	Y	Y	Y	Y	
Sahin and Karadeniz[24]			Y	Y	Y	Y	Y	Y	Y	Y	
Sotoudehmanesh et al[25]			Y	Y	Y	Y	Y	Y	Y	Y	
Stamm[26]			Y	Y	Y	Y	Y	N	Y	Y	
Sun et al[27]			Y	Y	Y	Y	Y	Y	Y	Y	
Walters[28]			U	Y	Y	Y	Y	N	Y	N	

Abbreviations: Y, yes; N, no; U, unclear.
[a]The JBI critical appraisal checklist for cohort studies had 11 questions whereas the checklist for cross-sectional studies had eight questions.

TABLE 3 Exposure and outcomes in the included studies.

Study	Method of IPFD determination	IPFD parameter	Definition of fatty change of the pancreas	CVD determination	CVD parameter
Chan et al[13]	MRI	Fat fraction [a, b]	> 10.4%	CT	IHD [b]
Hannukainen et al[14]	MRS	Fat fraction [a]	NR	Coronary CT angiography, PET	IHD [b]
Jeong et al[15]	CT	Pancreas attenuation, [a]	NR	Digital fundus camera	Atherosclerotic retinopathy [a]
Kim et al[16]	CT	Pancreas attenuation [a, b]	Pancreatic attenuation below the median (36 Hounsfield units)	PWV	cIMT [a], carotid plaque [b], vascular stiffness [a]
Koo et al[17]	CT	Pancreas attenuation [a, b]	The lowest quintile of pancreas-to-spleen attenuation ratio	CT	Calcification of vessels [b]
Kul et al[18]	US	Echogenicity of the pancreas [b]	Increased echogenicity compared with the kidneys	US, transthoracic echocardiography	aIMT [a], echocardiographic parameters [a]
Li et al[19]	MRI	Fat fraction [b]	≥10.3%	PWV	Vascular stiffness [b]
Meloni et al[20]	MRI	Fat fraction [a, b]	≥6.6%	MRI	Cardiac complications [b]
Ordulj et al[21]	CT	Pancreas attenuation [a]	NR	CT	Calcification of vessels [b]
Ozturk et al[22]	US	Echogenicity of the pancreas [b]	Increased echogenicity compared with the kidneys	US, PWV	cIMT, vascular stiffness [a]
Sahin et al[23]	US	Echogenicity of the pancreas [b]	Increased echogenicity compared with the kidneys	Conventional invasive coronary angiography	IHD [a]
Sahin and Karadeniz[24]	US	Echogenicity of the pancreas [b]	Increased echogenicity compared with the kidneys	US	cIMT [a]
Sotoudehmanesh et al[25]	EUS	Echogenicity of the pancreas [b]	Increased echogenicity compared with the spleen	EUS	aIMT [a], IHD [b]
Stamm[26]	Post-mortem examination	Histology [a]	>25% fatty replacement of the pancreatic parenchyma	Post-mortem examination	Atherosclerosis [b]
Sun et al[27]	CT	Pancreas attenuation [a, b]	The pancreas-to-spleen attenuation ratio ≤ 0.72	US	Carotid plaque [b]
Walters[28]	Post-mortem examination	Histology [a]	Partial or total fatty replacement of the pancreatic parenchyma	Post-mortem examination	Atherosclerosis [b]

Abbreviations: aIMT, aortic intima-media thickness; cIMT, carotid intima-media thickness; CT, computed tomography; CVD, cardiovascular disease; EUS, endoscopic ultrasound; IHD, ischemic heart disease; IPFD, intra-pancreatic fat deposition; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NR, not reported; PET, positron emission tomography; PWV, pulse wave velocity; US, ultrasound.
[a]Continuous variable.
[b]Categorical variable.

without it, had a significantly higher frequency of IHD – defined as myocardial infarction and history of coronary artery bypass graft (18.6% vs 8.2%; $p = 0.03$).[25] Chan et al investigated the association between IPFD and IHD – defined as coronary artery stenosis on coronary angiogram or CT coronary angiography.[13] Out of 631 individuals, 20 (3.2%) were newly diagnosed with IHD during the 10-year follow-up period. The incidence of IHD was nearly two times higher among individuals with fatty change of the pancreas than those without it, though the conventional level of statistical significance was not reached (5.4% vs 2.8%; $p = 0.17$).[13]

Hannukainen et al investigated the relationship of IPFD with IHD (defined as stenosis and atherosclerosis greater than 30% in at least one major coronary artery).[14] There were eight individuals with IHD, 14 individuals with nonischemic form of heart disease, and eight individuals without heart disease. No statistically significant difference between the three groups in terms of IPFD was reported ($p > 0.05$).[14] Sahin et al studied the association between fatty change of the pancreas and the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score – a widely used angiographic marker of IHD complexity, in 99 individuals with IHD.[23] The score was significantly higher in individuals with fatty change of the pancreas than those without it ($p < 0.001$). Further, the presence of a fatty change of the pancreas was a significant independent predictor of increased SYNTAX score (OR: 3.934; 95% CI: 1.657–9.339; $p = 0.002$).[23]

Meloni et al found that individuals with cardiac complications had a significantly higher IPFD than those without complications ($p = 0.002$).[20] Twenty individuals had at least one cardiac

complication, including heart failure in five individuals, arrhythmia in ten individuals (supraventricular in eight individuals, ventricular in two individuals), heart failure and supraventricular arrhythmia in three individuals, and pulmonary hypertension in two individuals. No individual with cardiac complications had normal IPFD. Fifty-six individuals developed myocardial fibrosis, including one individual who had an ischemic pattern. Individuals with myocardial fibrosis, compared to individuals without it, had a significantly higher IPFD ($p = 0.002$).[20]

3.3 | Relationship of fat in the pancreas with diseases of arteries, arterioles, and capillaries

Five studies investigated the association between IPFD and atherosclerosis, calcification of vessels, or atherosclerotic retinopathy.[15,17,21,26,28] Of them, two autopsy studies reported on the relationship between IPFD and the presence of atherosclerosis.[26,28] Stamm showed a statistically significant association ($p < 0.05$) between the presence of fatty change of the pancreas and severe generalized atherosclerosis (observed in 27/112, 24% of cadavers) in consecutive individuals without diseases of the exocrine pancreas.[26] Walters found severe generalized atherosclerosis in 56 out of 200 (28%) cadavers and fatty change of the pancreas was present in 43 (76.8%) of the 56 cadavers.[28]

Two studies investigated the relationship between fat in the pancreas and calcification of vessels.[17,21] In a large community-based cohort, Koo et al showed that the prevalence of carotid artery calcification was significantly higher in individuals with fatty change of the pancreas than those without it (46% vs 26%; $p < 0.001$).[17] The association remained statistically significant even after adjustment for age, sex, obesity, hypertension, dyslipidemia, smoking history, and family history of heart disease in first-degree relatives (OR: 1.265; 95% CI: 1.003–1.596; $p = 0.047$).[17] Calcifications in the thoracic aorta ($p = 0.387$), abdominal aorta ($p = 0.568$), coronary ($p = 0.591$), iliac ($p = 0.636$), renal ($p = 0.964$), celiac ($p = 0.847$), and superior mesenteric arteries ($p = 0.099$) were not significantly associated with fatty change of the pancreas after adjustment for the above-mentioned covariates, though all were significantly associated in the unadjusted analysis ($p < 0.001$ for all).[17] In a small cohort of Emergency Department patients, Ordulj et al found that IPFD was not associated with calcifications of the abdominal aorta ($p = 0.903$), superior mesenteric artery ($p = 0.143$), and common iliac artery ($p = 0.147$).[21] As this retrospective study relied on the availability of abdominal CT, calcifications in carotid and coronary arteries were not investigated.[21]

One study investigated the relationship between IPFD and atherosclerotic retinopathy.[15] Jeong et al found that IPFD was significantly associated with retinopathy (OR: 2.977; 95% CI: 1.143–7.757; $p = 0.03$) in non-obese individuals, after adjustment for age, sex, and HbA1c levels. By contrast, IPFD was not significantly associated with retinopathy in individuals with obesity ($p = 0.99$). While the prevalence of retinopathy in individuals with and without obesity was very similar (42% vs 41%; $p = 0.86$), the prevalence of retinopathy was significantly associated with the degree of IPFD ($p = 0.03$).[15]

3.4 | Relationship of fat in the pancreas with subclinical atherosclerosis

3.4.1 | Aortic intima-media thickness

Two studies investigated the relationship between fat in the pancreas and aortic intima-media thickness.[18,25] Sotoudehmanesh et al reported that individuals with fatty change of the pancreas had a significantly higher aortic intima-media thickness than individuals without it (1.38 mm vs 1.19 mm; $p = 0.01$).[25] Moreover, with each 1 mm increase in aortic intima thickness, the likelihood of having fatty change of the pancreas increased by a factor of 2.45 (95% CI: 1.05–5.78). Kul et al found a significantly higher aortic intima-media thickness in individuals with fatty change of the pancreas when compared with individuals without it (1.12 mm vs. 0.93 mm; $p < 0.001$).[18] The association remained statistically significant after accounting for age, BMI, hypertension, diabetes, sex, low-density lipoproteins, triglycerides, dyslipidemia, smoking, family history of IHD, and urea ($p = 0.024$).[18] A meta-analysis was conducted to investigate the association between fatty change of the pancreas and aortic intima-media thickness (Figure 2). Two studies encompassing 331 individuals were eligible,[18,25] and the meta-analysis showed that there was a significant association between the presence of fatty change of the pancreas and increased aortic intima-media thickness (mean difference: 0.19 mm; 95% CI: 0.12–0.26; $p < 0.001$). There was no statistical heterogeneity ($I^2 = 0\%$).

3.4.2 | Carotid intima-media thickness and plaque

Three studies reported on the relationship between fat in the pancreas and carotid intima-media thickness.[16,22,24] Ozturk et al showed in the unadjusted analysis that carotid intima-media thickness was significantly higher in individuals with severe fatty change of the pancreas when compared to those without it (0.47 mm vs 0.41 mm; $p = 0.035$).[22] Sahin and Karadeniz found that carotid intima-media thickness was significantly higher in individuals with fatty change of the pancreas when compared to those without it (0.51 mm vs 0.45 mm; $p < 0.01$).[24] A multivariable analysis found that fatty change of the pancreas was significantly associated with increased carotid intima-media thickness (OR: 3.078; 95% CI: 1.531–6.190; $p = 0.002$), after adjusting for age, hypertension, diabetes, sex, low-density lipoproteins, triglycerides, dyslipidemia, smoking, glucose, and urea.[24] Kim et al reported on the relationship between fatty change of the pancreas and subclinical atherosclerosis in T2DM individuals with and without obesity.[16] Subclinical atherosclerosis in the carotid artery was defined as either a carotid intima-media thickness ≥ 0.9 mm or carotid plaque. In the non-obese group, individuals with fatty change of the pancreas had a significantly higher probability for subclinical atherosclerosis (after adjusting for age, sex, and BMI) compared to individuals without it (OR: 3.12; 95% CI: 1.20–8.08; $p < 0.05$). In the obese group, the prevalence of subclinical atherosclerosis was not statistically different between individuals with versus without fatty change

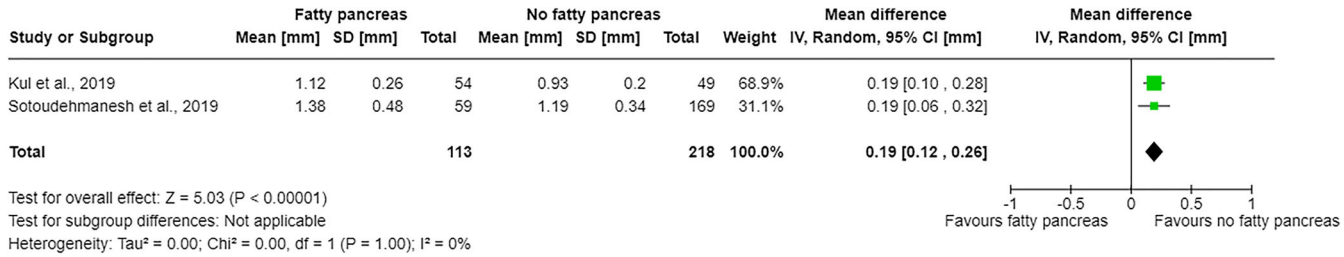

FIGURE 2 Relationship between fatty change of the pancreas and aortic intima-media thickness. Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation.

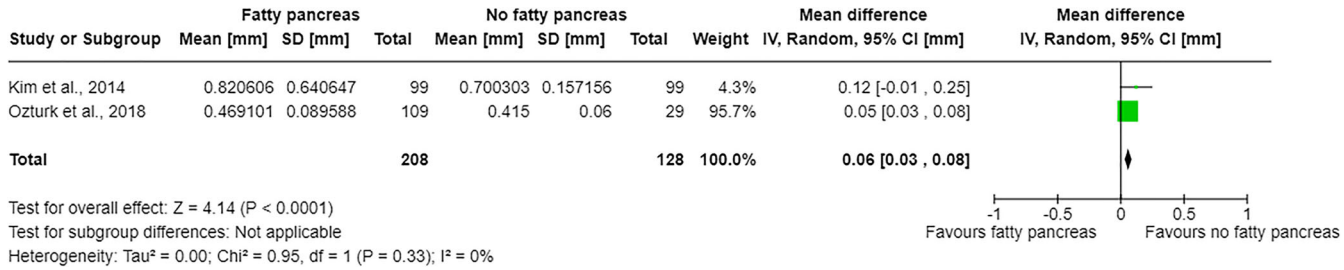

FIGURE 3 Relationship between fatty change of the pancreas and carotid intima-media thickness. Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation. *Note*: Aggregated data from two subgroups (i.e., individuals with and without obesity) in the study by Kim et al are presented.

of the pancreas ($p > 0.05$). The findings did not change materially when individuals were re-grouped according to the presence or absence of visceral adiposity.[16] A meta-analysis was conducted to investigate the association between fatty change of the pancreas and carotid intima-media thickness (Figure 3). Two studies encompassing 336 individuals were eligible,[16,22] and the meta-analysis showed a significant association between the presence of fatty change of the pancreas and increased carotid intima-media thickness (mean difference: 0.06 mm; 95% CI: 0.03–0.08; $p < 0.001$). There was no statistical heterogeneity ($I^2 = 0\%$).

Two studies investigated the association between fat in the pancreas and carotid plaque.[16,27] Sun et al reported that, after adjusting for age, sex, smoking, diabetes, hypertension, obesity, total cholesterol, triglycerides, and high-density lipoproteins, IPFD was significantly associated with carotid plaque (OR: 3.15; 95% CI: 1.47–6.73; $p = 0.003$).[27] When the study participants were categorized into hypoechoic and non-hypoechoic plaque groups, IPFD was significantly associated with carotid hypoechoic plaque (OR: 1.82; 95% CI; 1.09–3.02; $p = 0.02$).[27] Kim et al found a significantly higher frequency of carotid plaque in non-obese individuals with fatty change of the pancreas as compared with non-obese individuals without it (68% vs 31%; $p < 0.001$).[16] No significant difference in terms of frequency of carotid plaque was observed between obese individuals with fatty change of the pancreas and those without it ($p = 0.611$). Similar pattern of association between fatty change of the pancreas and carotid plaque was observed in the presence ($p = 0.439$) and absence ($p = 0.004$) of visceral adiposity.[16]

3.4.3 | Vascular stiffness

Three studies investigated the relationship between IPFD and vascular stiffness (as determined by PWV).[16,19,22] Kim et al reported that vascular stiffness was significantly associated with IPFD ($p = 0.001$).[16] Moreover, after adjusting for age, sex, and BMI, vascular stiffness was significantly higher in individuals with fatty change of the pancreas than those without it (1800 cm/s vs 1660 cm/s; $p = 0.042$).[16] Li et al found that individuals with fatty change of the pancreas had a significantly higher vascular stiffness than those without it (1159.68 (1087–1249.62) cm/s vs 1109.5 (1032.37–1167.79) cm/s; $p = 0.032$).[19] Further, fatty change of the pancreas and vascular stiffness were significantly correlated ($r = 0.19$; $p = 0.031$). After adjusting for age, smoking, BMI, blood pressure, lipid profile, liver enzymes, fasting plasma glucose, homeostasis model assessment of insulin resistance, and HbA1c, fatty change of the pancreas was significantly associated with high PWV (OR: 3.17; 95% CI: 1.05–9.58; $p = 0.041$). When compared to individuals with low PWV (defined as PWV ≤ 1159 cm/s), individuals with high PWV had significantly higher IPFD ($p = 0.003$) and prevalence of fatty change of the pancreas ($p = 0.006$).[19] Ozturk et al showed in the unadjusted analysis that PWV was significantly higher in individuals with severe fatty change of the pancreas when compared to those without it (890 cm/s vs 730 cm/s; $p < 0.001$).[22] A meta-analysis was conducted to investigate the association between fatty change of the pancreas and vascular stiffness (Figure 4). Two studies encompassing 336 individuals were eligible,[16,22] and the meta-analysis showed a significant

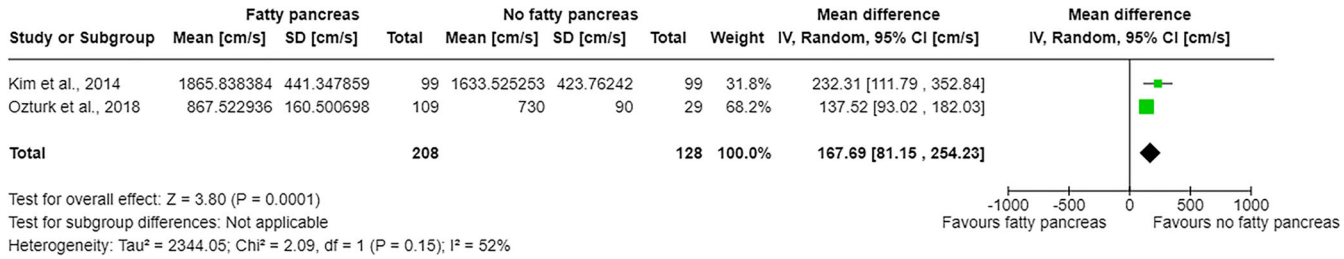

FIGURE 4 Relationship between fatty change of the pancreas and vascular stiffness. Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation. *Note*: Brachial-ankle pulse wave velocity was used in the study by Kim et al. Carotid-femoral pulse wave velocity was used in the study by Ozturk et al. Aggregated data from two subgroups (i.e., individuals with and without obesity) in the study by Kim et al are presented.

association between the presence of fatty change of the pancreas and increased vascular stiffness (mean difference: 167 cm/s; 95% CI: 81–254; $p < 0.001$). The statistical heterogeneity was moderate ($I^2 = 52\%$).

4 | DISCUSSION

Circumstantial evidence of the relationship between high IPFD and CVD has long been available. Earlier research demonstrated the connection of high IPFD with T2DM and metabolic syndrome – well-known risk factors for CVD.[29–35] Further, the PANcreatic Diseases Originating from intRa-pancreatic fAt (PANDORA) hypothesis postulated that high IPFD is a key driver of T2DM (as well as other common diseases of the pancreas).[36] More recently, the Atherosclerotic Cardiovascular Disease score was shown to be independently associated with fatty change of the pancreas (determined with the use of state-of-the-art 3.0 Tesla MRI) in a prospective cohort study of 324 individuals.[37] This score is endorsed by the American College of Cardiology and the American Heart Association and it estimates a 10-year risk of IHD based on diabetic status, blood pressure, cholesterol levels, medication use, age, sex, race, and smoking status. A multivariable analysis (accounting for age, sex, dyslipidemia, and tobacco smoking) demonstrated that IPFD was significantly ($p = 0.001$) associated with high (defined in the study as ≥7.5%) risk score. Moreover, high risk score was significantly more common among individuals with fatty change of the pancreas as compared to those without it (60% vs 29%; $p < 0.001$). Notably, hepatic fat was not significantly associated with the Atherosclerotic Cardiovascular Disease score.[37] The present systematic review takes the fields of obesity and cardiology further by synthesizing, for the first time, the available evidence on 'hard', objectively measured, and clinically meaningful CVD outcomes in the context of fatty change of the pancreas.

The body of literature on the topic was accumulated over more than a half-century and encompassed more than 7000 individuals. High IPFD was associated with some of the CVD outcomes but not others (Table 4). Meta-analysis showed significant associations between the presence of fatty change of the pancreas and subclinical

TABLE 4 Directions of the relationship between fat in the pancreas and CVD in the included studies.

CVD outcome	Study	Relationship
Heart diseases		
IHD	Sahin et al[23]	↑
	Sotoudehmanesh et al[25]	↑
	Chan et al[13]	→
	Hannukainen et al[14]	→
Cardiac complications	Meloni et al[20]	↑
Diseases of arteries, arterioles, and capillaries		
Atherosclerosis	Stamm[26]	↑
	Walters[28]	↑
Calcification of vessels[a]	Koo et al[17]	↑
	Ordulj et al[21]	→
Atherosclerotic retinopathy	Jeong et al[15]	↑
Subclinical atherosclerosis		
Aortic intima-media thickness	Kul et al[18]	↑
	Sotoudehmanesh et al[25]	↑
Carotid intima-media thickness	Kim et al[16]	↑
	Sahin and Karadeniz [24]	↑
	Ozturk et al[22]	↑
Carotid plaque	Kim et al[16]	↑
	Sun et al[27]	↑
Vascular stiffness	Kim et al[16]	↑
	Li et al[19]	↑
	Ozturk et al[22]	↑

Note: ↑ = statistically significant positive relationship; → = no statistically significant relationship. As reported in primary studies and based on at least one CVD outcome.
Abbreviations: CVD, cardiovascular disease; IHD, ischemic heart disease.
[a]Four vascular beds (neck, thorax, abdomen, and pelvis) were investigated in the study by Koo et al. Two vascular beds (abdomen and pelvis) were investigated in the study by Ordulj et al.

atherosclerosis, as consistently evidenced by increased carotid intima-media thickness, aortic intima-media thickness, and vascular stiffness. The majority of the included studies also showed a significant association of high IPFD with diseases of arteries, arterioles, and capillaries – most notably, atherosclerosis observed in both earlier hospital autopsy and modern large population-based studies of individuals who underwent CT for preventive health screening.[17,26,28] The findings in regard to the associations between fatty change of the pancreas and heart diseases were less consistent. In fact, arguably the most robust study (a 2022 prospective longitudinal cohort study with 10-year follow-up) included in the present systematic review did not show a statistically significant association of fat in the pancreas with newly-developed IHD.[13] However, this might have been attributed to insufficient statistical power in regard to this secondary outcome as IHD developed in only 3.2% (20/631) of study participants. At the same time, it is worth noting that the incidence of IHD was approximately two times higher in individuals with fatty change of the pancreas (5.4%, 5 out of 93) than those without it (2.8%, 15 out of 538).[13] Insufficient statistical power might have also precluded the identification of a statistical significance in a 2020 study of 55 donors, though a trend for the prevalence of IHD to be higher in individuals with histologically confirmed fatty change of the pancreas was noted.[38] In a 2016 study of individuals undergoing CT angiography that found the association between IPFD and CVD did not reach the conventional level of statistical signifcance,[14] the mean IPFD was approximately two times higher in individuals with IHD than those without IHD. The absence of statistical significance might have been attributed to the small sample size and the use of MRS to measure fat in the pancreas (which is known to result in high inter-individual variability and is considered inferior to MRI when it comes to measuring IPFD).[14,36]

Many earlier studies attributed fatty change of the pancreas merely to general adiposity and the sequence of events that can follow, which includes excess visceral adiposity, leading to adipocyte infiltration of non-adipose tissues, and eventual fat deposition within organs.[39,40] However, our present systematic review suggests that the relationship between fatty change of the pancreas and CVD may be independent of general adiposity. Specifically, in individuals without general adiposity, high IPFD was strongly associated with atherosclerotic retinopathy[15] and fatty change of the pancreas was strongly associated with intima-media thickness of vessels after adjustment for BMI.[16,18] Moreover, IPFD was significantly associated with carotid plaque and carotid artery calcification after accounting for BMI.[17,27] This is in line with the findings of our 2017 systematic review of 14,804 individuals that showed in a meta-regression analysis that simple anthropometric measures (such as BMI and waist circumference) were not significantly associated with fatty change of the pancreas.[9] A 2020 case–control study showed that higher IPFD was accompanied by a significantly less dense pancreatic arterial tree in individuals with T2DM (who had a mean BMI of 27 kg/m^2) than controls ($p = 0.003$), suggesting that IPFD may directly influence the arterial tree in the hepato-pancreato-biliary area.[41] Taken together, the above findings support the tenet that fatty change of the pancreas has implications for CVD beyond those attributed to general adiposity. It is believed that fatty change of the pancreas leads to lipotoxicity – the deleterious effects resulting from the accumulation of lipids in non-adipose tissues (as described in the PANDORA hypothesis),[36] which represents a plausible causal link supported by biological mechanisms. When IPFD exceeds a threshold in a given individual, it can lead to inflammation within the pancreatic microenvironment (independent of general adiposity) and the associated release of proinflammatory cytokines.[42,43] These cytokines may lead to excess glycaemic variability, high-density lipoprotein dysfunction, endothelial cell dysfunction – which are all known contributors to the development of microvascular and macrovascular pathologies and all have recently been demonstrated to significantly associate with IPFD.[44–50] Deeper insights into the mechanistic links between fatty change of the pancreas and cardiovascular pathologies, independent of general adiposity, will likely be gained in the not-too-distant future.

This systematic review has several limitations that need to be acknowledged. First, the determination of IPFD differed between the included studies, with various methods used. The gold-standard imaging modality for non-invasive determination of IPFD is MRI,[6,36] but only three included studies used it.[13,19,20] Future studies investigating the relationship between IPFD and CVD should preferably employ MRI. Second, the overwhelming majority of included studies were cross-sectional. This makes it impossible to identify cause-and-effect relationships. While purposely designed adequately powered longitudinal cohort studies would be most preferred, an acceptable starting point could be the use of genetic variants as natural experiments (because genetic variants are fixed at conception) in the already available large cohorts.[51] For example, several Mendelian randomization studies capitalizing on the UK Biobank have elegantly established the causal role of high IPFD in the development of pancreatitis and pancreatic cancer.[52–55] Last, 10 out of the 16 studies were conducted in Asia,[13,15,16,18,19,22–25,27] which might have influenced the findings of the systematic review as the phenotypic variation in the presentation of cardiovascular and pancreatic diseases may differ among ethnic groups. Studies on IPFD and CVD from other parts of the world are therefore encouraged.

5 | CONCLUSION

With the growing global burden of CVD, this systematic review identified the available data on the association between IPFD and CVD. It considerably strengthened the evidence base suggesting that fatty change of the pancreas may be an important, yet currently underappreciated, risk factor for CVD. As fatty change of the pancreas is significantly associated with subclinical atherosclerosis, there is a potential for using high IPFD as an early risk factor for CVD, in particular among individuals without conventional risk factors (e.g., general adiposity). The link between fatty change of the pancreas and clinically manifest IHD warrants a sufficiently powered study. Further exploration of the relationship between IPFD and CVD could refine risk assessment strategies and contribute to a more comprehensive approach to the prevention and management of CVD.

AUTHOR CONTRIBUTIONS

Conceptualization, M.S.P.; data acquisition, Y.Z.; analysis and interpretation of data, Y.Z., Y.L.; drafting of the manuscript, Y.Z.; critical revision of the manuscript for important intellectual content, Y.L., M.S.P.; study supervision, M.S.P.

ACKNOWLEDGMENTS

This study was part of the COSMOS programme. The authors would like to thank Rayna Dewar (University of Auckland, New Zealand) for her contribution to the literature search. Open access publishing facilitated by The University of Auckland, as part of the Wiley - The University of Auckland agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Zhang Y, Liu Y, Petrov MS. Relationship of fat in the pancreas with cardiovascular disease: A systematic review and meta-analysis. *Obesity Reviews*. 2025; e13914. doi:10.1111/obr.13914