BMJ Open

Systematic review and meta-analysis assessing the status of carotid intima–media thickness and lipid profiles in type 2 diabetes mellitus

Reneilwe Given Mashaba ,[1,2] Wendy Phoswa,[1] Eric Maimela,[2] Sogolo Lebelo,[1] Perpetua Modjadji,[1,3,4] Kabelo Mokgalaboni [1]

To cite: Mashaba RG, Phoswa W, Maimela E, *et al*. Systematic review and meta-analysis assessing the status of carotid intima–media thickness and lipid profiles in type 2 diabetes mellitus. *BMJ Open* 2024;**14**:e087496. doi:10.1136/bmjopen-2024-087496

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-087496).

Received 11 April 2024
Accepted 27 September 2024

For numbered affiliations see end of article.

Correspondence to
Mr Kabelo Mokgalaboni; mokgak@unisa.ac.za

ABSTRACT

Objectives Carotid intima–media thickness (CIMT) is a measurement for subclinical atherosclerosis and has been associated with overall cardiovascular diseases, especially in type 2 diabetes mellitus (T2DM). We aimed to assess the status of carotid health and lipid profile in T2DM.

Design This systematic review and meta-analysis synthesised data published from clinical studies.

Data sources Google Scholar, PubMed and Scopus were searched from inception to 18 January 2024.

Eligibility criteria for selecting studies Studies conducted in patients with T2DM and those without T2DM were included. Studies conducted in T2DM adults evaluating carotid status and lipid profile were considered.

Data extraction and synthesis Two authors independently used standardised methods to comprehensively search, screen and extract data from all relevant studies. The risk of bias was assessed using the Newcastle-Ottawa checklist. Meta-analysis was conducted using Review Manager and metaHun through random effects models. The random effect model was used due to high heterogeneity.

Results Evidence was analysed from 57 studies with a sample size of 29 502 (8254 T2DM and 21 248 people without T2DM). There was a significantly higher CIMT, with a standardised mean difference (SMD) of 1.01 (95% CI 0.75, 1.26, p<0.00001). Additionally, there was an elevated triglyceride (TG) (SMD=1.12, 95% CI 0.82, 1.41, p<0.00001), total cholesterol (TC), (SMD=0.24, 95% CI 0.02, 0.46, p=0.03) and low-density lipoprotein-cholesterol (LDL-C), (SMD=0.35, 95% CI 0.11, 0.59, p=0.004) in patients with T2DM compared with those without T2DM. Furthermore, a significant decrease in high-density lipoprotein cholesterol (HDL-C) was observed in the T2DM compared with people without T2DM, SMD=−0.79, 95% CI −0.96, −0.62, p<0.00001). Age, body mass index and hypertension were associated with increased CIMT and TG and decreased HDL-C in T2DM. Additionally, age, gender and hypertension were associated with an increased LDL-C in T2DM.

Conclusion Our findings suggest that an increased CIMT is accompanied by increased TG, TC, LDL-C and HDL-C reduction in patients with T2DM.

PROSPERO registration number CRD42023451731.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review and meta-analysis comprehensively used three databases to search for literature.
⇒ Independent researchers used the Newcastle-Ottawa guideline to assess the quality of all observational studies.
⇒ The study was performed in phases by independent researchers, including search, selection, extraction and analysis.
⇒ The mean, SD and sample size for each study for individual parameters were used to estimate the effect size using Review Manager and metaHun.
⇒ Meta-regression was used to assess the relationship between age, gender, body mass index and hypertension with carotid intima–media thickness.

INTRODUCTION

Diabetes mellitus (DM) is a complex chronic condition of carbohydrate metabolism characterised by the body's inability to produce or respond to insulin.[1 2] Patients with DM often present with comorbidities such as hypertension, dyslipidaemia, insulin resistance, obesity and hyperglycaemia, which increase their risk of cardiovascular disease (CVD)-related mortality.[3 4] Recent evidence has demonstrated that patients with DM are at high risk of developing CVDs and associated complications compared with pre-diabetes and non-DM.[5] CVDs are made up of disorders of the heart and blood vessels, including coronary heart disease, cerebrovascular disease, heart failure and atherosclerosis, as a result of dyslipidaemia and chronic inflammation.[6 7] Additionally, a subclass of DM, type 2 DM (T2DM), is commonly known to have a high risk of secondary conditions such as anaemia due to impaired haematological indices.[8] This may further increase the risk of CVDs in this group of patients.

Chronic inflammation and dyslipidaemia are more prevalent in patients with DM and have a negative impact on cardiovascular health.[9–11] Chronic inflammation, as a classic feature of T2DM, has been associated with atherosclerosis and intimal calcification.[12 13] Carotid intima–media thickness (CIMT) is associated with lipid accumulation and, therefore, serves as an ideal marker of subclinical atherosclerosis and CVD in patients with DM.[3 14 15] CIMT is defined as the distance from the lumen–intima interface to the media–adventitia interface of the arterial wall, mainly measured noninvasively through ultrasonography images of the carotid arteries.[16] This ultrasonic test uses higher-resolution images, which detect the early stages of CIMT thickening.[17] Previous evidence reported that an increase in CIMT by 0.1 mm increases the relative risk of ischaemic heart disease by 15% and cerebral vascular disease by 18%.[3]

CIMT values are associated with hypercholesterolaemia regardless of genetic aetiology and predisposition.[18] The previous meta-analyses showed an elevated CIMT in prediabetes and DM[19 20]; however, analysed evidence was collected from clinical trials with small sample sizes in different clinical studies, especially in T2DM. This poses a question about the statistical power of such evidence. Other studies have shown no significant differences in CIMT status among T2DM and people without T2DM.[7 21–23] More recently, researchers have shown decreased left and right internal CIMT in T2DM compared with people without T2DM.[24] These conflicting results, especially with more recent evidence showing reduced CIMT compared with old evidence, prompt an investigation into the status of CIMT among T2DM, which could assist in the assessment of its contribution to the development of secondary CVD.

On the other hand, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) contribute to the development of atherosclerosis.[25] Therefore, impaired lipid profiles in T2DM may contribute to secondary complications among patients with T2DM. While this is commonly known, conflicting results have emerged from various researchers, with some showing no elevation in lipid profile and others showing no significant difference in T2DM.[21 23 26 27]

DM has been reported to have a negative impact on the CIMT and the lipids profile. Notably, an increased CIMT has been associated with the development of various CVDs. However, based on the conflicting findings on CIMT status in T2DM, the contribution of CIMT to dyslipidaemia and CVDs remains unclear. Therefore, it is important to research the extent of T2DM patients' risk of developing future CVDs to manage the condition best. In this study, we reviewed and quantitatively analysed evidence from existing clinical studies to evaluate the status of CIMT and lipid profiles in patients with T2DM.

METHODOLOGY

Registrations and reporting

This systematic review and meta-analysis protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42023451731 and subsequently published.[28] This systematic review and meta-analysis is reported according to the guidelines outlined by the Meta-analysis of Observational Studies in Epidemiology[29] (online supplemental file 1).

Patient and public involvement

Not applicable, no participants were recruited as the study used data from published studies.

Aims and PECOS criteria

This study aims to assess the overall status of CIMT and lipid profile in T2DM.

PECOS is outlined as follows: population includes adult patients with T2DM, exposure is DM, comparator is people without T2DM and outcomes included CIMT and lipid profile status. In terms of designs, cross-sectional studies, case controls, and prospective and retrospective cohorts were all included.

Search strategy

Independent authors (RGM and KM) systematically searched literature on Google Scholar, PubMed and Scopus databases from inception to 18 January 2024. The following medical subject heading (MeSH) terms and boolean operators were used to identify studies: carotid artery intima–media thickness OR CIMT AND lipid profile AND T2DM. The MeSH/keywords were modified for each database. Furthermore, reference lists of the relevant studies that were retrieved were also screened to identify additional eligible studies. Any disagreement in the search was resolved by an independent author (WP).

Study selection: inclusion and exclusion criteria

The studies were included if they were conducted in patients with T2DM, reporting CIMT and any lipid parameter (TG, TC, LDL-C and HDL-C) in T2DM, published in English. In cases where a study had multiple T2DM groups, we combined data to get the overall mean from two T2DM groups.

In contrast, the studies were excluded if they were not conducted in T2DM or did not specify the form of DM, preclinical studies on T2DM, did not measure CIMT status, measured lipid parameters without CIMT status, studies without data about CIMT in one group, studies on treatment, published in other language, abstract, letters to the editor, retracted studies, grey literature including preprints and theses or dissertation.

Data extraction and quality assessment

The authors (RGM and KM) independently extracted the following data from eligible studies: name of the first author, year of publication, country, sample size, age, DM status, the mean and SD for TC, TG, HDL-C,

LDL-C and CIMT. The Excel sheet was used to capture all extracted data. The main findings of the studies were also summarised. A third independent author (WP) verified data extracted by RGM and KM to reduce biases. Quality was assessed by following guidelines from the Newcastle-Ottawa Scale (NOS).[30] This method considers three main domains: selection, comparability and outcome across different study designs. This activity was undertaken independently by RGM and KM with WP as arbitrator in case of inconsistencies.

Data-analysis

Data extracted in this study were analysed by using Review Manager (V.5.4) and metaHun (http://softmed.hacettepe.edu.tr/metaHUN/) (accessed on 19 January 2024). We used the data (sample size, mean±SD) to explore the change of all outcomes (CIMT, lipid profiles) in T2DM compared with people without T2DM. In case median and ranges were given in the study, such data were converted to mean and SD following guidelines by.[31 31] Similarly, if the mean and SE (SEM) were reported, SD was estimated using the formula SEM=SD/√n. The effect sizes were reported as standardised mean differences (SMD) and 95% CIs. The magnitude of effect size was categorised as small, medium and large when equivalent to 0.2, 0.5 and 0.8, respectively. P values of <0.05 were regarded as statistically significant. We used the I^2 statistic test to assess statistical heterogeneity.[32] The I^2 values of <50% and >75% were classified as minimal and substantial statistical heterogeneity, respectively. Due to heterogeneity, a random-effect model meta-analysis was performed. Sensitivity analysis was conducted using a one-study exclusion procedure to evaluate the stability of our effect size. Publication bias was evaluated graphically using funnel plots and statistically with Egger's regression tests. Meta-regression was also performed to find the association between the outcomes and moderators, such as age, gender, body mass index (BMI), hypertension status and study design.

RESULTS

Literature search and selection of included records

A total of 214 records were retrieved using the following search engines and databases: Google Scholar (n=18), PubMed (n=85) and Scopus (n=111). The search is presented in online supplemental table 1. Mendeley reference manager (V.2.98.0) was used to exclude seven duplicate records retrieved from the search. Before full-text screening, 29 records were excluded due to irrelevant titles, abstracts and keywords. Following full-text screening, additional sets of records were excluded. Among them, 44 had no control groups, 23 were irrelevant populations, 22 were studies on treatments, 15 had no main outcomes of interest, 7 had no sufficient data, 4 reviews, 2 protocols and 1 letter to the editor. Additionally, one study was conducted in an animal model of T2DM, one was retracted from the journal and one full text was not retrieved. Finally, 57 studies[7 14 15 21–27 33–79] met the inclusion criteria for the present study and were included in this meta-analysis (figure 1).

General features of included studies

Online supplemental table 2 summarises the overview characteristics of included studies from peer-reviewed journals published between 1995 and 2024. Evidence from these 57 studies with a total sample size of 29 502 (8254 T2DM and 21 248 people without T2DM) was included in the current analysis. Among the included T2DM, 4090 (49.6%) participants were male, while 4164 (50.4%) were females. However, it is important to note that the two studies did not specify the gender distribution of the enrolled population. The age of participants was reported in 56 studies; the median and IQR age of T2DM was 56.05 (51.18–60.05) years, confirming that the meta-analysis included adults only. The BMI of the T2DM group was 28.6 (25.5–30.5) kg/m^2, suggesting an overweight status in T2DM. It is noteworthy to indicate that BMI was not reported in at least four studies.

The majority of included evidence was conducted from China,[14 22 25 38 61 68–72 78] Turkey,[26 27 34 36 44 45 50 63 65 67 76 77] Egypt,[15 40 53 59 60 66 74] Iran,[7 23 46] Italy,[33 42 52] Spain,[35 43] India,[48] Nigeria,[47] Pakistan,[75] Iraq,[24] Romania,[73] Germany,[51] Japan,[21] Hungary,[49] Australia,[58] South Africa,[55] Slovenia,[56 62] Sweden,[64] the USA,[57] Saudi Arabia,[79] Denmark,[54] Mexico[37] and the Netherlands.[39 41] 46 studies were cross-sectional,[7 14 15 21–23 26 27 33–46 48–53 55–59 63–65 69–77 79] 5 were cohorts and[24 25 54 62 78] 6 were case controls.[47 60 61 66–68]

The quality of the included studies

Among the included studies, all cross-sectional studies were classified as good quality, scoring at least 6 and 7 stars (online supplemental table 3). On the other hand, all included cohorts were also rated as having good quality as they scored between 6 and 7 stars out of possible eight scores (online supplemental table 4). Similarly, the case controls scored 8 stars and were classified as good quality (online supplemental table 5).

Status of CIMT in patients with T2DM compared with people without T2DM

57 studies[7 14 15 21–27 33–79] with a sample size of 8254 patients with T2DM and 21 248 people without T2DM were included in the random effect meta-analysis of studies reporting CIMT. CIMT was significantly high in patients with T2DM compared with people without T2DM participants, SMD=1.01, 95% CI (0.75, 1.26), p<0.00001, (figure 2). The studies had significant heterogeneity (I^2=98%; p<0.00001). Sensitivity analysis was conducted following leave-one-out analysis; for CIMT, a notable change was observed when three studies were excluded,[58] SMD=0.91, 95% CI (0.65, 1.16), p=0.000,[24] SMD=1.10, 95% CI (0.90, 1.29), p=0.000 and SMD=0.95, 95% CI (0.71, 1.20), p=0.000.[55]

TGs in patients with T2DM compared with people without T2DM

50 studies[7 14 15 21–23 25–27 33–41 43 46–56 58–74 77–79] with 6954 patients with T2DM and 8484 people without T2DM that

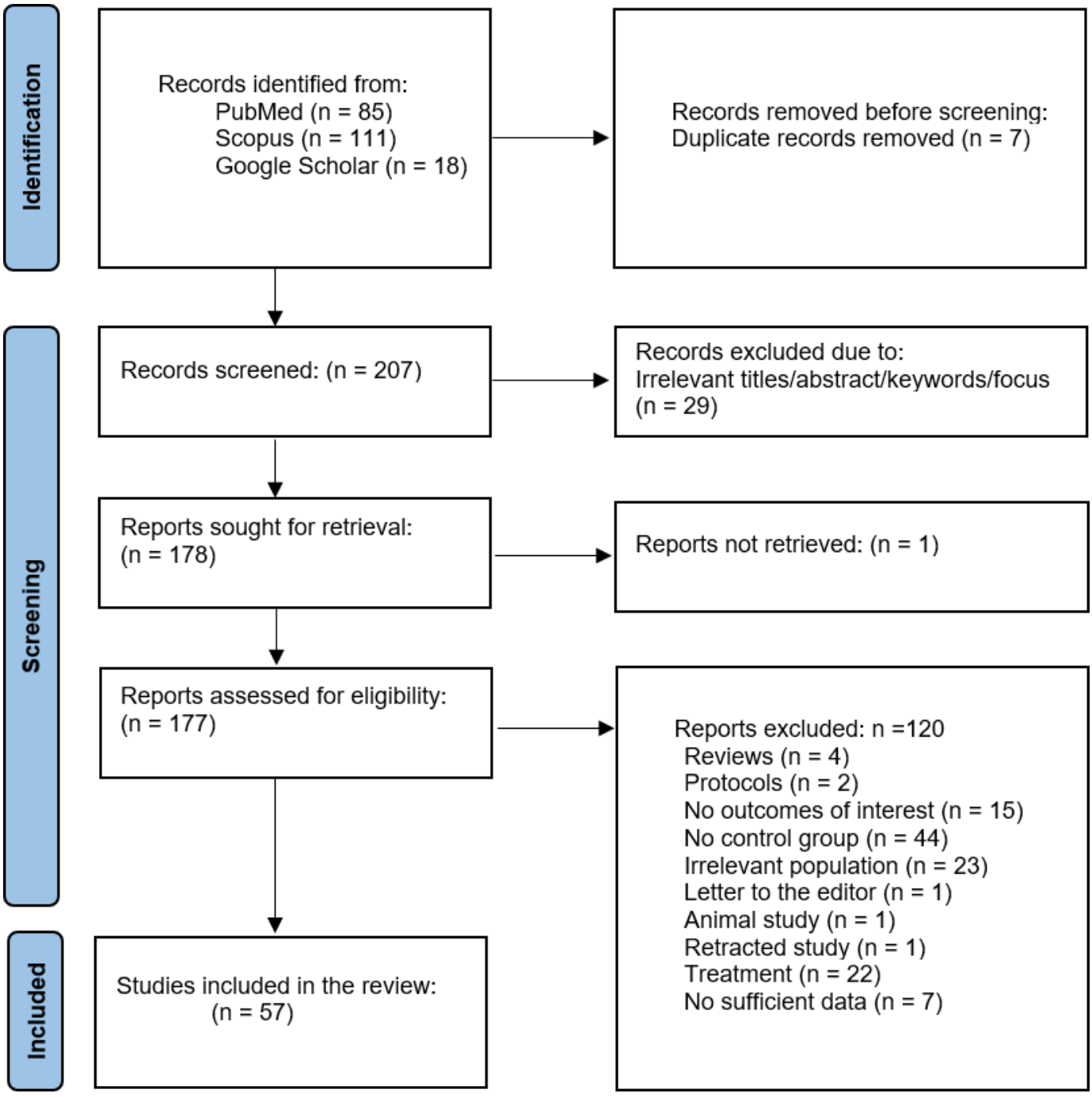

Figure 1 Flow diagram showing study selection and inclusion.

reported on TG were included in the meta-analysis. The levels of TG significantly increased in patients with T2DM compared with people without T2DM SMD=1.12, 95% CI (0.82, 1.41), p<0.00001 (figure 3). The studies had substantial heterogeneity (I^2=98%; p<0.00001). For the sensitivity analysis, the exclusion of two studies, Meyer *et al* and Káplár *et al*,[49 58] resulted in a change in effect size (SMD=1.03, 95% CI (0.74, 1.33), p=0.000) and SMD=1.02, 95% CI (0.74, 1.31, p=0.0000) respectively. Additionally, the exclusion of Kowall *et al*[51] yielded an effect size of SMD=1.05, 95% CI (0.81, 1.29), p=0.0000.

TC in patients with T2DM compared with people without T2DM

46 studies[7 14 15 21–23 25–27 33–41 46–50 53–62 65–74 77–79] with a sample size of 6072 patients with T2DM and 15 672 people without T2DM that assessed TC were included in this meta-analysis. The level of TC was significantly increased in T2DM compared with people without T2DM, SMD=0.24, 95% CI (0.02, 0.46, p=0.03) (online supplemental figure 1). However, the studies presented considerable heterogeneity (I^2=97%; p<0.00001). Sensitivity analysis showed that the exclusion of the study by Meyer *et al*[58] changed the effect size to SMD=0.14, 95% CI

Study or Subgroup	Patients With T2DM Mean	SD	Total	People Without T2DM Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
AbdelAal et al., 2021	0.99	0.23	50	0.636	0.103	25	1.7%	1.77 [1.21, 2.34]
Albu et al., 2010	0.91	0.17	33	0.76	0.137	21	1.7%	0.93 [0.36, 1.51]
Ali et al., 2018	0.95	0.21	150	0.72	0.19	60	1.8%	1.12 [0.80, 1.44]
Amouzegar et al., 2022	0.4176	0.1126	118	0.4176	0.1125	126	1.8%	0.00 [-0.25, 0.25]
Areej et al., 2023	0.6333	0.16536	60	0.57	0.14297	60	1.8%	0.41 [0.05, 0.77]
Bakirci et al., 2015	0.8	0.25	132	0.66	0.13	80	1.8%	0.66 [0.37, 0.94]
Bilgir et al., 2019	0.81	0.19	143	0.67	0.11	133	1.8%	0.89 [0.64, 1.14]
Bonora et al., 2005	1.44	0.15	56	1.19	0.15	58	1.7%	1.66 [1.23, 2.08]
Bulut et al., 2019	0.78	0.14	60	0.6	0.1	60	1.8%	1.47 [1.07, 1.87]
Catalan et al., 2015	0.7855	0.1398	106	0.7412	0.1159	99	1.8%	0.34 [0.07, 0.62]
Celik et al., 2014	0.92	0.22	100	0.8	0.22	31	1.8%	0.54 [0.13, 0.95]
Contreras-Rodriguez et al., 2015	0.6989	0.147	110	0.566	0.172	35	1.8%	0.86 [0.47, 1.26]
Dong et al., 2022	0.69	0.0909	69	0.67	0.1061	67	1.8%	0.20 [-0.14, 0.54]
Dullaart et al., 2012	0.88	0.2	80	0.77	0.09	40	1.8%	0.64 [0.25, 1.03]
Farrag et al., 2008	1.2783	0.2204	40	0.828	0.072	20	1.6%	2.40 [1.70, 3.09]
Flores-Guerrero et al., 2024	0.883	0.195	81	0.808	0.147	89	1.8%	0.44 [0.13, 0.74]
Gaudio et al., 2013	0.867	0.214	40	0.784	0.107	40	1.7%	0.49 [0.04, 0.93]
Gomez-Marcos et al., 2011	0.781	0.11	121	0.686	0.09	89	1.8%	0.93 [0.64, 1.22]
Gunes et al., 2021	0.65	0.13	49	0.54	0.1	45	1.7%	0.94 [0.51, 1.36]
Güneş et al., 2022	0.98	0.22	69	0.8	0.1	40	1.8%	0.96 [0.55, 1.37]
Guo et al., 2023	1.37	0.23	120	1.24	0.17	40	1.8%	0.60 [0.23, 0.96]
Güvener et al., 2000	0.72	0.19	70	0.54	0.14	52	1.8%	1.05 [0.67, 1.43]
Heidari et al., 2014	0.78	0.2	107	0.66	0.14	101	1.8%	0.69 [0.41, 0.97]
Joseph et al., 2020	0.54	0.15	62	0.49	0.1	60	1.8%	0.39 [0.03, 0.75]
Káplár et al., 2016	0.672	0.148	103	0.602	0.128	98	1.8%	0.50 [0.22, 0.78]
Kocaoğlu et al., 2016	0.82	0.18	114	0.76	0.17	100	1.8%	0.34 [0.07, 0.61]
Koc et al., 2018	0.85	0.17	58	0.7	0.13	27	1.7%	0.94 [0.46, 1.42]
Kowall et al., 2012	0.94	0.13	189	0.83	0.13	1938	1.8%	0.85 [0.69, 1.00]
Kozakova et al., 2019	0.782	0.129	191	0.668	0.139	94	1.8%	0.86 [0.60, 1.12]
Lachine et al., 2016	0.93	0.2	90	0.7	0.15	90	1.8%	1.30 [0.97, 1.62]
Li et al., 2016	1.18	0.29	320	0.71	0.13	250	1.8%	2.01 [1.81, 2.21]
Lu et al., 2015	0.9188	0.1357	245	0.5908	0.112	148	1.8%	2.57 [2.30, 2.84]
Lundby-Christensen et al., 2010	0.8	0.131	28	0.679	0.105	30	1.7%	1.01 [0.46, 1.56]
Lv et al., 2017	0.8278	0.15	69	0.68	0.09	28	1.7%	1.08 [0.61, 1.55]
Macharia et al., 2014	0.98	0.073	142	0.77	0.048	349	1.8%	3.72 [3.42, 4.02]
Majidi et al., 2021	0.83	0.12	42	0.79	0.1	42	1.7%	0.36 [-0.07, 0.79]
Merlo et al., 2016	0.958	0.194	595	0.89	0.212	200	1.8%	0.34 [0.18, 0.50]
Metcalf et al., 2000	0.8	0.182	921	0.74	0.22	11976	1.8%	0.28 [0.21, 0.34]
Meyer et al., 2004	0.88	0.02	45	0.68	0.02	45	1.1%	9.91 [8.38, 11.45]
Nafakhi et al., 2023	0.87	0.15	198	78	17	586	1.8%	-5.24 [-5.55, -4.93]
Naguib et al., 2021	0.074	0.012	50	0.04	0.0004	25	1.6%	3.42 [2.68, 4.16]
Naguib et al., 2022	0.06	0.01	75	0.05	0.02	40	1.8%	0.70 [0.30, 1.09]
Okafor et al., 2018	0.83	0.16	54	0.74	0.1	54	1.8%	0.67 [0.28, 1.06]
Pan et al., 2019	6.81	1.36	114	5.89	1.03	98	1.8%	0.75 [0.47, 1.03]
Popović et al., 2016	20.66	13.48	426	14.17	8.87	137	1.8%	0.52 [0.32, 0.71]
Sahin et al., 2014	0.8	0.1	171	0.72	0.1	61	1.8%	0.80 [0.50, 1.10]
Strawbridge et al., 2016	0.758	0.145	901	0.738	0.141	2470	1.8%	0.14 [0.06, 0.22]
Taniguchi et al., 2002	0.71	0.14	51	0.7	0.096	23	1.7%	0.08 [-0.42, 0.57]
Taniwaki et al., 1999	1.004	0.372	271	0.64	0.182	285	1.8%	1.25 [1.07, 1.43]
Tawfeek et al., 2014	0.93	0.2	30	0.64	0.08	30	1.7%	1.88 [1.27, 2.49]
Uçar et al., 2020	0.73	0.2	40	0.64	0.19	40	1.7%	0.46 [0.01, 0.90]
Wang et al., 2019	0.785	0.0545	120	0.65	0.0898	120	1.8%	1.81 [1.51, 2.11]
Yafei et al., 2019	0.79	0.16	76	0.58	0.08	30	1.7%	1.47 [1.00, 1.93]
Yiu et al., 2013	0.96	0.2	100	0.86	0.14	150	1.8%	0.60 [0.34, 0.86]
Zhang et al., 2014	0.6265	0.1691	50	0.5685	0.1226	41	1.8%	0.38 [-0.03, 0.80]
Zhang et al., 2017	1.1	0.2	149	0.6	0.1	72	1.8%	2.86 [2.47, 3.25]
Zheng et al., 2018	0.82	0.1422	200	0.54	0.08	100	1.8%	2.23 [1.93, 2.53]
Total (95% CI)			**8254**			**21248**	**100.0%**	**1.01 [0.75, 1.26]**

Heterogeneity: Tau² = 0.95; Chi² = 3218.46, df = 56 (P < 0.00001); I² = 98%
Test for overall effect: Z = 7.64 (P < 0.00001)

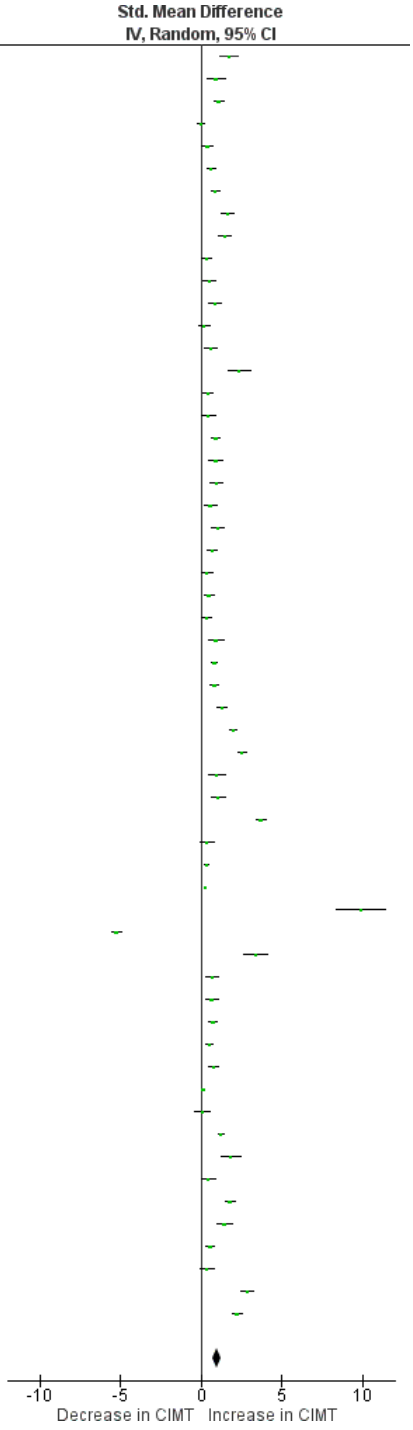

Figure 2 Forest plot reflecting the status of carotid intima–media thickness (CIMT) in T2DM compared with people without T2DM. T2DM, type 2 diabetes mellitus.

(−0.07, 0.34), p=0.18. Both Zhang *et al*[22] and Naguib *et al*[60] led to SMD=0.19, 95% CI (−0.02, 0.40), p=0.077. Lastly, the exclusion of Káplár *et al*[49] changed the effect size to SMD=0.30, 95% CI (0.10, 0.50), p=0.032.

LDL-C in patients with T2DM compared with people without T2DM

43 studies[7 14 15 21–23 26 27 34–38 40 43 46–50 52–65 67–72 77–79] with 7194 patients with T2DM and 18 159 people without T2DM that investigated LDL-C were included in this meta-analysis. The level of LDL-C was significantly increased in T2DM compared with people without T2DM SMD=0.35, 95% CI (0.11, 0.59), p=0.004 (online supplemental figure 2). The studies had significant heterogeneity (I^2=98%; p<0.00001). For sensitivity analysis, the exclusion of one study at a time revealed a change in effect size, for instance, Káplár *et al*[49] had an SMD of 0.22 (95% CI 0.00, 0.44), p=0.05, Meyer *et al*[58] reported an SMD of 0.24 with 95% CI (0.01, 0.48), p=0.041,[22 22] SMD=0.29, 95% CI

Study or Subgroup	Patients With T2DM Mean	SD	Total	People Without T2DM Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
AbdelAal et al., 2021	197.32	44.16	50	137.92	26.18	25	1.9%	1.50 [0.96, 2.04]
Albu et al., 2010	143	13	33	108.3	9.1	21	1.8%	2.93 [2.14, 3.73]
Ali et al., 2018	132.17	35.54	150	100.87	9.19	60	2.0%	1.02 [0.71, 1.34]
Amouzegar et al., 2022	105.15	6.85	118	96.59	14.15	126	2.0%	0.76 [0.50, 1.02]
Bilgir et al., 2019	242.88	195.53	143	138.97	59.8	133	2.0%	0.71 [0.46, 0.95]
Bonora et al., 2005	1.85	0.86	56	1.41	0.68	58	2.0%	0.56 [0.19, 0.94]
Bulut et al., 2019	210	145	60	88	30	60	2.0%	1.16 [0.77, 1.55]
Catalan et al., 2015	130.95	16.47	106	103	11.22	99	2.0%	1.96 [1.63, 2.30]
Celik et al., 2014	187.65	105.15	100	140.78	77.49	31	2.0%	0.47 [0.06, 0.88]
Contreras-Rodriguez et al., 2015	201.92	39.58	110	99.11	12.13	35	2.0%	2.92 [2.41, 3.43]
Dong et al., 2022	1.69	0.848	69	1.37	0.5985	67	2.0%	0.43 [0.09, 0.77]
Dullaart et al., 2012	1.68	0.7625	80	1.28	0.792	40	2.0%	0.51 [0.13, 0.90]
Farrag et al., 2008	121.33	23.69	40	117.1	23.8	20	1.9%	0.18 [-0.36, 0.71]
Flores-Guerrero et al., 2024	1.7	0.7548	81	1.41	0.8289	89	2.0%	0.36 [0.06, 0.67]
Gomez-Marcos et al., 2011	135.9	75.28	121	114.57	61.09	89	2.0%	0.31 [0.03, 0.58]
Guo et al., 2023	1.54	0.32	120	1.05	0.27	40	2.0%	1.58 [1.18, 1.98]
Güvener et al., 2000	166.7	66.3	70	152.9	71.68	52	2.0%	0.20 [-0.16, 0.56]
Heidari et al., 2014	195.62	107.98	107	169.65	74.62	101	2.0%	0.28 [0.00, 0.55]
Joseph et al., 2020	1.5	0.28	62	1.5	0.19	60	2.0%	0.00 [-0.35, 0.35]
Káplár et al., 2016	2.87	0.29	103	1.53	0.11	98	1.9%	6.03 [5.37, 6.69]
Kocaoğlu et al., 2016	173	108	114	150	101	100	2.0%	0.22 [-0.05, 0.49]
Koc et al., 2018	162.73	81.77	58	152.9	64.75	27	2.0%	0.13 [-0.33, 0.58]
Kowall et al., 2012	1.58	0.21	189	1.07	0.12	1938	2.1%	3.91 [3.72, 4.10]
Kozakova et al., 2019	1.32	0.82	191	1.25	0.61	94	2.0%	0.09 [-0.15, 0.34]
Lachine et al., 2016	146.28	52.31	90	131.95	65.54	90	2.0%	0.24 [-0.05, 0.53]
Li et al., 2016	1.44	0.59	320	1.42	0.59	250	2.1%	0.03 [-0.13, 0.20]
Lu et al., 2015	1.93	0.23	245	1.23	0.16	148	2.0%	3.38 [3.07, 3.70]
Lundby-Christensen et al., 2010	1.45	0.55	28	1.33	0.57	30	2.0%	0.21 [-0.31, 0.73]
Lv et al., 2017	2.17	1.14	69	1.05	0.39	28	2.0%	1.13 [0.66, 1.59]
Macharia et al., 2014	1.8	1	142	1.4	0.8	349	2.1%	0.46 [0.27, 0.66]
Majidi et al., 2021	143.09	17.49	42	128.7	15.27	42	2.0%	0.87 [0.42, 1.32]
Merlo et al., 2016	1.9	0.24	595	1.31	0.18	200	2.1%	2.60 [2.40, 2.81]
Meyer et al., 2004	1.88	0.1	45	1.28	0.1	45	1.7%	5.95 [4.97, 6.93]
Naguib et al., 2021	195.66	38.77	50	106.92	18.88	25	1.9%	2.62 [1.97, 3.26]
Naguib et al., 2022	2.14	1	75	1.39	0.56	40	2.0%	0.85 [0.45, 1.25]
Okafor et al., 2018	112.1	13.4	54	108.8	12.1	54	2.0%	0.26 [-0.12, 0.64]
Pan et al., 2019	1.92	1.61	114	1.17	0.33	98	2.0%	0.62 [0.35, 0.90]
Popović et al., 2016	1.94	1.1147	595	1.94	1.1147	200	2.1%	0.00 [-0.16, 0.16]
Sahin et al., 2014	169.5	97.6	171	145.03	69.6	61	2.0%	0.27 [-0.03, 0.56]
Strawbridge et al., 2016	1.91	1.82	901	1.47	0.9	2470	2.1%	0.36 [0.29, 0.44]
Taniguchi et al., 2002	121	8	51	114	3	23	2.0%	1.01 [0.49, 1.53]
Taniwaki et al., 1999	1.54	0.88	271	1.34	0.79	285	2.1%	0.24 [0.07, 0.41]
Tawfeek et al., 2014	173.52	57.82	30	97	12.02	30	1.9%	1.81 [1.20, 2.42]
Uçar et al., 2020	177.7	101.02	40	142.85	55.72	40	2.0%	0.42 [-0.02, 0.87]
Wang et al., 2019	1.37	0.23	120	1.05	0.14	120	2.0%	1.68 [1.38, 1.97]
Yafei et al., 2019	177.5	101	76	101.2	36.7	30	2.0%	0.86 [0.42, 1.30]
Yiu et al., 2013	1.5	0.8	100	1.3	0.7	150	2.0%	0.27 [0.01, 0.52]
Zhang et al., 2014	1.13	0.87	50	1.02	0.65	41	2.0%	0.14 [-0.27, 0.55]
Zhang et al., 2017	2.08	0.58	149	1.3	0.64	72	2.0%	1.30 [0.99, 1.60]
Zheng et al., 2018	1.86	0.42	200	1.31	0.17	100	2.0%	1.54 [1.27, 1.81]
Total (95% CI)			**6954**			**8484**	**100.0%**	**1.12 [0.82, 1.41]**

Heterogeneity: Tau² = 1.10; Chi² = 2782.59, df = 49 (P < 0.00001); I² = 98%
Test for overall effect: Z = 7.40 (P < 0.00001)

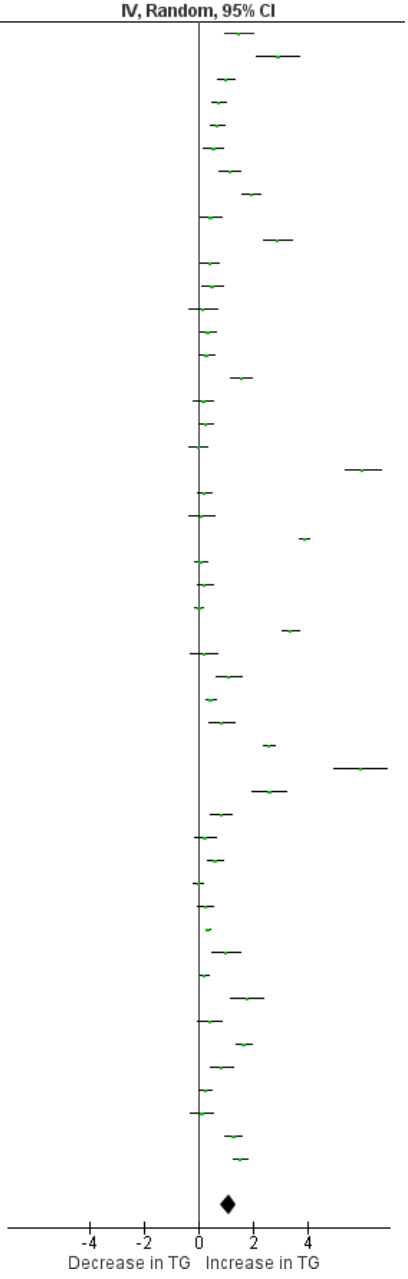

Figure 3 Forest plot of studies reporting triglyceride (TG) levels in patients with T2DM compared with people without T2DM. T2DM, type 2 diabetes mellitus.

(0.06, 0.53), p=0.013 and last Amouzegar *et al*[7] showed an SMD=0.42, 95% CI (0.19, 0.65), p=0.000.

HDL-C in patients with T2DM compared with people without

A total of 47 studies[7 14 15 21–23 26 27 33–41 43 46–65 67–72 77–79] encompassing 7600 patients with T2DM and 18506 people without T2DM reporting on HDL-C were included in the meta-analysis. The random effect model meta-analysis revealed a significantly decreased HDL-C level in patients with T2DM compared with people without T2DM, SMD=−0.79, 95% CI (−0.96, −0.62), p<0.00001 (online supplemental figure 3). The studies had significant heterogeneity (I^2=96%; p<0.00001). In sensitivity analysis, only the exclusion of the study by Káplár *et al*[49] resulted in a shift in effect size, SMD=−0.65 (0.80, −0.50), p=0.0000. Exclusion of Majidi *et al*[23] resulted in an SMD of −0.84, 95% CI (−1.02, −0.66), p=0.0000. Exclusion of Meyer *et al*[58] yielded an SMD of −0.71, 95% CI (−0.88, −0.54), p=0.0000. The exclusion of both Naguib *et al*[60] and Wang *et al*[72] changed the effect size to SMD=−0.73, 95% CI (0.90, 0.56), p=0.0000.

Publication bias

For studies that assessed the status of CIMT in T2DM, an evaluation of publication bias using funnel plots revealed some potential level of biases (online supplemental figure 4A); interestingly, this was supported statistically by the Egger's regression test (Z score=6.70, p<0.05).

Funnel plots showed evidence of bias on TG (online supplemental figure 4B); this was also supported by the Egger's regression test (Z score 4.6, p<0.05). Funnel plots depicted potential evidence of biases for TC (online supplemental figure 4C); this was supported statistically by the Egger's regression test (Z score=6.20, p=0.000). Visual inspection of LDL-C through a funnel plot showed bias (online supplemental figure 4D). Interestingly, this was supported by Egger's regression test results (Z score=6.89, p=0.000). Lastly, there was evidence of bias across studies that evaluated HDL-C and showed publication bias through funnel plots (online supplemental figure 4E), which was corroborated by the Egger's regression test (Z score =–14.81, p=0.0000).

Meta-regression output

We explored the association between CIMT and lipid profile status in T2DM. The selected moderators included age, gender, BMI, hypertension and study design. Meta-regression based on age suggests there is a direct relationship between CIMT and age in T2DM (p=0.001). Similarly, the same observation was noted in BMI (p=0.035) and hypertension status (p=0.000). This implies that age, BMI and hypertension status are significant moderators (online supplemental table 6). However, gender was not a significant moderator (p=0.266) (online supplemental table 6). Interestingly, using the study design as a moderator was also found to be a significant moderator (p=0.001) (online supplemental table 6). For TG, all moderators except for gender were notable (p<0.05) factors associated with elevated TG in T2DM (online supplemental table 6). No significant association was observed between TC and all moderators (p>0.05) (online supplemental table 6). For LDL-C, age, gender and hypertension status were significant moderators (p<0.05) associated with an increased LDL-C (online supplemental table 6). Moreover, age, gender, BMI, hypertensive status and study design were significant moderators (p<0.05) associated with reduced HDL-C levels among patients with T2DM (online supplemental table 6).

DISCUSSION

The present study systematically reviewed and quantitatively analysed existing literature on the status of CIMT and lipid profiles in patients with T2DM. This study found that CIMT was higher in patients with T2DM than those without T2DM. Additionally, TG, TC and LDL-C levels were increased in the T2DM group than in people without T2DM. Furthermore, a significant reduction in HDL-C levels in patients with T2DM compared with people without T2DM was observed. In support of the present study, Zhou *et al* reported an increase in CIMT in patients with T2DM.[80] Our meta-regression has revealed that age, BMI and hypertension are some of the factors that contribute to an increased CIMT among T2DM. This is also supported by a previous study that reports an association between CIMT and age and BMI.[47] Indeed, different biological ageing measures correlate with T2DM vascular complications, possibly extending the range of risk factors driving atherosclerosis in T2DM.[81 82] In the current study, no association was noted between increased CIMT and gender, suggesting gender does not have an impact on the status of CIMT among T2DM. This evidence is aligned with previous reports, as no significant relationship was observed between increased CIMT and gender in T2DM.[47]

Hyperglycaemia associated with T2DM has been reported as an independent risk factor for increased CIMT, thus increasing the risk of CVD, including ischaemic stroke.[83 84] An increased CIMT in patients with T2DM may be attributed to hyperglycaemia-induced endothelial dysfunctions, which promote chronic inflammation and further increase the risk of atherosclerosis.[85 86] Inflammatory cytokines can also result in the accumulation of immune cells in the arterial wall, thus contributing to the thickening of the artery.[87] More recently, a systematic review and meta-analysis was conducted in DM to evaluate the status of CIMT. Although the study found an increased CIMT status in DM, it was conducted in children with T1DM.[88] The latter results may not be translatable to adult T2DM populations, especially as it has been observed that age has a significant association with increased CIMT among patients with T2DM. An increased CIMT in T2DM remains a challenge due to the associated cardiovascular complications such as atherosclerosis.[89] The exact mechanism of artery thickness in T2DM is not fully understood. However, it is assumed that hyperglycaemic states in T2DM may contribute to CIMT thickening through the formation of advanced glycation end products (AGEs). These AGEs result from elevated blood glucose and bind to the proteins in the arterial walls, thereby reducing wall elasticity and contributing to arterial stiffness.[90]

On the other hand, elevated blood glucose impairs the endothelium's inner layer, making it more receptive to foam cells and lipids, thereby promoting the development of atherosclerotic plaques.[86] The present plagues induce intima thickening. Another mechanism by which DM is associated with the thickening of CIMT thickening is due to elevated insulin levels experienced by people with DM, and this promotes the growth of smooth muscle cells in the arterial wall,[91] resulting in CIMT thickening. As observed in the current study, hypertension is associated with increased CIMT in T2DM, and increased blood pressure impairs the arterial walls, promoting atherosclerosis. Therefore, primary measures must be put in place to control hypertension in T2DM to curb associated secondary complications.

The present study found a significant increase in TG, TC and LDL-C levels between the T2DM and those without T2DM, further supporting previous evidence. For instance, previous studies reported increased LDL-C and TC levels in T2DM compared with people without T2DM.[92 93] Age, gender and hypertension were found to be associated with an increased LDL-C. Usually, an

increased LDL-C in T2DM is induced by inflammation, thereby impairing lipid metabolism.[94] This, subsequently, results in an increased LDL-C production and a reduced clearance from the bloodstream. This results in high LDL-C in the blood. Age and gender contribute to an increased LDL-C; primarily, ageing slows down metabolism and reduces liver function, thereby slowing down LDL-C removal.[95 96] As women reach menopause, their oestrogen levels decline, resulting in an increased HDL-C.[97] Although small dense LDL-C was not assessed in the current study due to lack of data, the evidence from the literature has indicated that these particles can infiltrate the arterial wall and promote foam cell formation and arterial plaques.[98] According to Al Mansour, the prevalence of high TC was 23.7% in patients with T2DM.[99]

Additionally, 2Acuña *et al*[92] reported that 46.7% of patients with T2DM had TC levels in the upper limits. Moreover, Paquet *et al* reported consistently high serum TC levels in patients with uncontrolled T2DM.[93] The evidence of the contribution of high serum TC and LDL-C to atherosclerosis has been reported extensively in the literature. In another meta-analysis, higher serum TC and LDL-C were regarded as the leading cause of coronary atherosclerosis and an increased risk of CVD.[100]

While the present study found an increased TG in patients with T2DM compared with those without T2DM, this agrees with evidence from other clinical studies that reported increased TG in patients with T2DM.[101] Insulin resistance in patients with T2DM has been reported to promote lipogenesis,[102] including increased TG synthesis,[103] which has been associated with cardiovascular complications such as atherosclerosis and the thickening of CIMT.[104]

The level of HDL-C decreased in the T2DM group compared with those without T2DM. According to Agbaje *et al*, low HDL-C was associated with CIMT progression.[105] In DM, HDL-C particles undergo conformation changes that impair their function.[106] Additionally, T2DM has been reported to alter HDL-C metabolism, leading to decreased HDL-C production and function, resulting in low HDL-C in circulation.[107] One of the central features of T2DM is insulin resistance; this disrupts lipid metabolism, resulting in low HDL-C.[108] In contrast to the current study, an increase in plasma HDL-C has been regarded as a novel therapeutic option to reduce the risk of T2DM.[109] Interestingly, a previous report by Mokgalaboni *et al* showed an impaired lipid profile in patients with T2DM.[10] This further supports the observation from the current findings that patients with T2DM have an impaired lipid profile, which predisposes them to the risk of cardiovascular complications. Our results suggest that patients with T2DM are at high risk of developing dyslipidaemia and CVDs due to impaired lipid profiles and increased CIMT, respectively. Therefore, CIMT and lipid profile monitoring should be considered in T2DM treatment and management protocols.

Strength and limitations

The study involved independent authors in search, screening and extraction to avoid bias. The study's strength was that different databases were used by qualified researchers who searched for studies independently. The age of included participants across all studies was 56.05 (51.18–60.05) years, indicating that they were adults. Moreover, the overall quality of the included studies was classified as good, as determined by the NOS guideline. Interestingly, a protocol for this study was also registered with the PROSPERO to allow transparency. Both graphical and statistical analyses were used to assess publication bias. Some of the limitations to acknowledge in this study include a lack of information about the duration of T2DM, which could limit our interpretation of results according to duration, as it is known to impact the progression of T2DM. The median (IQR) BMI was 28.6 (25.5–30.5) kg/m^2, classified as overweight.

Consequently, these findings may not apply to younger participants who fall outside the overweight category. The included studies did not report the small dense LDL-C levels, which were not preplanned in the protocol phase and thus were not considered in the current analysis. The evidence reflected substantial heterogeneity; however, meta-regression analysis was performed to find the association between all outcomes and possible moderators (age, gender, BMI, hypertension and study design).

CONCLUSIONS AND RECOMMENDATIONS

Despite the conflicting evidence from individual studies, the overall evidence from this study shows that patients with T2DM have an elevated CIMT compared with those without T2DM. This was coupled with a pronounced increase in TG, TC and LDL-C among patients with T2DM. Furthermore, a significant reduction in HDL-C was also observed. The study underscored the presence of dyslipidaemia in patients with T2DM. Dyslipidaemia in patients with T2DM predisposes them to a heightened risk of developing secondary CVD compared with those without T2DM. This risk is substantiated by the elevated CIMT observed in the T2DM compared with those without T2DM in this study. The evidence synthesised in this study shows a high risk of subclinical atherosclerosis and dyslipidaemia among T2DM; these results can be considered when developing therapies against subclinical atherosclerosis and CVDs.

Author affiliations
[1]Life and Consumer Sciences, University of South Africa College of Agriculture and Environmental Sciences, Florida, Gauteng, South Africa
[2]DIMAMO Population Health Research Centre, University of Limpopo - Turfloop Campus, Mankweng, South Africa
[3]Non-Communicable Diseases Research Unit, South African Medical Research Council, Cape Town, South Africa
[4]Department of Public Health, School of Health Care Sciences, Sefako Makgatho Health Sciences University, Ga-Rankuwa, Pretoria, South Africa

Acknowledgements KM is partially funded by the Research Development Grants for nGAP Scholars (NGAP23022780506) and South African National Research Foundation Special Transformation Awards (NSTA231114163486).

Contributors Conceptualisation, KM and RGM; methodology, RGM, KM and WP; software, RGM and KM; validation, RGM, KM, WP, SL and PM; formal analysis, RGM and KM; investigation, RGM and KM; resources, KM; data curation, RGM and KM, writing-original draft preparation, RGM and KM.; writing-review and editing, RGM, KM, WP, EM, SL and PM; visualisation, RGM, KM, WP, EM, SL and PM; supervision, KM and WP; project administration, KM; funding acquisition, KM. All authors have read and agreed to the published version of the manuscript. KM is the guarantor of this study.

Funding This study was funded by National Research Foundation (NGAP23022780506, NSTA231114163486).

Disclaimer Funders have no role in the conceptualisation, preparation, data analysis and conclusion reached in this manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. The secondary data supporting this manuscript is included in the online supplemental material. Data extracted from each study are available at the request of the corresponding author.

ORCID iDs
Reneilwe Given Mashaba http://orcid.org/0000-0001-6235-2325
Kabelo Mokgalaboni http://orcid.org/0000-0002-3224-7433

REFERENCES

1 Rajas F, Gautier-Stein A, Mithieux G. Glucose-6 Phosphate, A Central Hub for Liver Carbohydrate Metabolism. *Metabolites* 2019;9:282.
2 American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2022;45:S17–38.
3 Aswini D, Shriram T, Lavanya D, *et al*. Association of carotid intima media thickness with cardio vascular risk factors in type 2 diabetes mellitus patients- a cross sectional study. *Eur J Mol Clin Med* 2023;10:635–42.
4 Yen F-S, Wei JC-C, Chiu L-T, *et al*. Diabetes, hypertension, and cardiovascular disease development. *J Transl Med* 2022;20:1–12.
5 Gateva A, Assyov Y, Karamfilova V, *et al*. Common carotid artery intima media thickness (CIMT) in patients with prediabetes and newly diagnosed type 2 diabetes mellitus. *J Diabetes Complications* 2024;38:108766.
6 Joseph JJ, Deedwania P, Acharya T, *et al*. Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association. *Circulation* 2022;145:e722–59.
7 Amouzegar A, Mirzaasgari Z, Mehrabi A, *et al*. Association of monocyte/high-density lipoprotein cholesterol ratio and the carotid intima-media thickness in diabetic patients. *BMC Endocr Disord* 2022;22:323.
8 Mokgalaboni K, Mabusela MS, Moraba MM. Haematological Indices and Anaemia in Patients with Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis. *SN Compr Clin Med* 2020;2:899–908.
9 Ren H, Zhu B, Zhao Z, *et al*. Neutrophil to high-density lipoprotein cholesterol ratio as the risk mark in patients with type 2 diabetes combined with acute coronary syndrome: a cross-sectional study. *Sci Rep* 2023;13:7836.
10 Mokgalaboni K, Dludla PV, Nyambuya TM, *et al*. Monocyte-mediated inflammation and cardiovascular risk factors in type 2 diabetes mellitus: A systematic review and meta-analysis of pre-clinical and clinical studies. *JRSM Cardiovasc Dis* 2020;9:2048004019900748:2048004019900748:.
11 Dregan A, Charlton J, Chowienczyk P, *et al*. Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. *Circulation* 2014;130:837–44.
12 Dube P, DeRiso A, Patel M, *et al*. Vascular Calcification in Chronic Kidney Disease: Diversity in the Vessel Wall. *Biomedicines* 2021;9:404.
13 Kim TI, Guzman RJ. Medial artery calcification in peripheral artery disease. *Front Cardiovasc Med* 2023;10:1093355.
14 Lv Y, Zhang Y, Shi W, *et al*. The Association Between Endocan Levels and Subclinical Atherosclerosis in Patients With Type 2 Diabetes Mellitus. *Am J Med Sci* 2017;353:433–8.
15 Yafei S, Elsewy F, Youssef E, *et al*. Echocardiographic association of epicardial fat with carotid intima-media thickness in patients with type 2 diabetes. *Diab Vasc Dis Res* 2019;16:378–84.
16 Gaarder M, Seierstad T. Measurements of carotid intima media thickness in non-invasive high-frequency ultrasound images: the effect of dynamic range setting. *Cardiovasc Ultrasound* 2015;13:5.
17 Ayoola OO, Bolarinwa RA, Onakpoya OH, *et al*. Intima-media thickness of the common carotid arteries as a marker of retinopathy and nephropathy in sickle cell disease. *Ultrasonography* 2020;39:79–84.
18 Gałąska R, Kulawiak-Gałąska D, Chmara M, *et al*. Carotid intima–media thickness (IMT) in patients with severe familial and non-familial hypercholesterolemia: The effect of measurement site on the IMT correlation with traditional cardiovascular risk factors and calcium scores. *Cardiol J* 2021;28:271–8.
19 Sun Y-P, Cai Y-Y, Li H-M, *et al*. Increased carotid intima-media thickness (CIMT) levels in patients with type 1 diabetes mellitus (T1DM): A meta-analysis. *J Diabetes Complications* 2015;29:724–30.
20 Brohall G, Odén A, Fagerberg B. Carotid artery intima-media thickness in patients with Type 2 diabetes mellitus and impaired glucose tolerance: a systematic review. *Diabet Med* 2006;23:609–16.
21 Taniguchi A, Nakai Y, Fukushima M, *et al*. Ultrasonographically assessed carotid atherosclerosis in Japanese type 2 diabetic patients: Role of nonesterified fatty acids. *Metab Clin Exp* 2002;51:539–43.
22 Zhang L, Yin J-K, Duan Y-Y, *et al*. Evaluation of carotid artery elasticity changes in patients with type 2 diabetes. *Cardiovasc Diabetol* 2014;13:1–10.
23 Majidi Z, Emamgholipour S, Omidifar A, *et al*. The circulating levels of CTRP1 and CTRP5 are associated with obesity indices and carotid intima-media thickness (cIMT) value in patients with type 2 diabetes: a preliminary study. *Diabetol Metab Syndr* 2021;13:14:14:.
24 Nafakhi H, Elwali HQ, Al-Sharea KMK, *et al*. Relationship of cardiovascular risk factors, pericardial fat, and carotid thickness with coronary plaque type in patients with diabetes mellitus. *J Diabetes Metab Disord* 2023;22:713–9.
25 Guo H-J, Li C-C, Bian X-Y, *et al*. Correlation study on the relationship between dyslipidemia and carotid intima-media thickness in patients with diabetes mellitus. *Pak J Med Sci* 2023;39:875–9.
26 Koc AS, Sumbul HE. Increased aortic intima-media thickness may be used to detect macrovascular complications in adult type II diabetes mellitus patients. *Cardiovasc Ultrasound* 2018;16:8:8:.
27 Güvener N, Tütüncü NB, Oto A, *et al*. Major determinants of the carotid intima-media thickness in type 2 diabetic patients: age and body mass index. *Endocr J* 2000;47:525–33.
28 Mashaba RG, Phoswa W, Maimela E, *et al*. Association of carotid intima-media thickness and dyslipidaemia in patients with type 2 diabetes: a protocol for systematic review and meta-analysis. *BMJ Open* 2024;14:e079209.
29 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting. *JAMA* 2008;283:2008–12.

30 Wells G, Shea B, Robertson J, *et al*. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis, 2014. Available: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
31 Wan X, Wang W, Liu J, *et al*. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
32 Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, *et al*. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* 2006;11:193–206.
33 Bonora E, Tessari R, Micciolo R, *et al*. Intimal-medial thickness of the carotid artery in nondiabetic and NIDDM patients. Relationship with insulin resistance. *Diabetes Care* 1997;20:627–31.
34 Bulut A, Avci B. Carotid intima-media thickness values are significantly higher in patients with prediabetes compared to normal glucose metabolism. *Medicine (Baltimore)* 2019;98:e17805.
35 Catalan M, Herreras Z, Pinyol M, *et al*. Prevalence by sex of preclinical carotid atherosclerosis in newly diagnosed type 2 diabetes. *Nutr Metab Cardiovasc Dis* 2015;25:742–8.
36 Celik M, Cerrah S, Arabul M, *et al*. Relation of asymmetric dimethylarginine levels to macrovascular disease and inflammation markers in type 2 diabetic patients. *J Diabetes Res* 2014;2014:139215:139215:.
37 Contreras-Rodríguez A, Gómez-Díaz RA, Tanus-Hajj J, *et al*. Carotid Intima-Media Thickness, Ankle-Arm Index, and Inflammation Profile in Mexican Patients with Early and Late Onset Type 2 Diabetes. *Res Inves Clin* 2015;67:240–9.
38 Dong Y, Liu J, Ma J, *et al*. The possible correlation between serum GRB2 levels and carotid atherosclerosis in patients with type 2 diabetes mellitus. *Front Endocrinol (Lausanne)* 2022;13:963191.
39 Dullaart RPF, Kappelle PJWH, de Vries R. Lower carotid intima media thickness is predicted by higher serum bilirubin in both non-diabetic and Type 2 diabetic subjects. *Clin Chim Acta* 2012;414:161–5.
40 Farrag W, Eid MAE. Association of the C242T polymorphism of the p22 phox gene with advanced carotid atherosclerosis in type 2 diabetes. *Mol Med Rep* 2008;1:679–84.
41 Flores-Guerrero JL, Been RA, Shalaurova I, *et al*. Triglyceride/HDL cholesterol ratio and lipoprotein insulin resistance Score: Associations with subclinical atherosclerosis and incident cardiovascular disease. *Clin Chim Acta* 2024;553:117737.
42 Gaudio A, Privitera F, Pulvirenti I, *et al*. The relationship between inhibitors of the Wnt signalling pathway (sclerostin and Dickkopf-1) and carotid intima-media thickness in postmenopausal women with type 2 diabetes mellitus. *Diab Vasc Dis Res* 2014;11:48–52.
43 Gómez-Marcos MA, Recio-Rodríguez JI, Rodríguez-Sánchez E, *et al*. Carotid Intima-Media Thickness in Diabetics and Hypertensive Patients. *Rev Esp Cardiol (Eng Ed)* 2011;64:622–5.
44 Gunes M, Temizkan S, Apaydin T, *et al*. Serum osteoprotegerin levels, endothelial function and carotid intima-media thickness in type 2 diabetic patients. *J Diabetes Complications* 2021;35:108073.
45 Güneş M, Kara Z, Yavuzer S, *et al*. Relationship Between Carotid Intima-Media Thickness and Osteoporosis in Type 2 Diabetic Patients: Cross-Sectional Study in the Third-Level Center. *Metab Syndr Relat Disord* 2022;20:592–8.
46 Heidari B, Fotouhi A, Sharifi F, *et al*. Elevated serum levels of pregnancy-associated plasma protein-A in type 2 diabetics compared to healthy controls: associations with subclinical atherosclerosis parameters. *Acta Med Iran* 2015;53:395–402.
47 Okafor EA, Adekanmi AJ, Atalabi OM. Relationship between Carotid Intima-Media Thickness and Diabetes Clinical Risk Factors among Normotensive Type 2 Diabetes Mellitus among Native Black African Population. *IJCM* 2018;09:203–19.
48 Joseph TP, Kotecha NS, Kumar H B C, *et al*. Coronary artery calcification, carotid intima-media thickness and cardiac dysfunction in young adults with type 2 diabetes mellitus. *J Diabetes Complications* 2020;34:107609.
49 Káplár M, Sweni S, Kulcsár J, *et al*. Mannose-Binding Lectin Levels and Carotid Intima-Media Thickness in Type 2 Diabetic Patients. *J Diabetes Res* 2016;2016:8132925.
50 Kocaoğlu İ, Kocaoğlu E, Arslan U, *et al*. Relationship between retinopathy and asymptomatic atherosclerosis determined by measurement of carotid intima-media thickness in patients with type 2 diabetes mellitus. *Turk Kardiyol Dern Ars* 2016;44:24–9.
51 Kowall B, Ebert N, Then C, *et al*. Associations between Blood Glucose and Carotid Intima-Media Thickness Disappear after Adjustment for Shared Risk Factors: The KORA F4 Study. *PLoS ONE* 2012;7:e52590.
52 Kozakova M, Morizzo C, Goncalves I, *et al*. Cardiovascular organ damage in type 2 diabetes mellitus: the role of lipids and inflammation. *Cardiovasc Diabetol* 2019;18.
53 Lachine NA, Elnekiedy AA, Megallaa MH, *et al*. Serum chemerin and high-sensitivity C reactive protein as markers of subclinical atherosclerosis in Egyptian patients with type 2 diabetes. *Ther Adv Endocrinol Metab* 2016;7:47–56.
54 Lundby-Christensen L, Almdal TP, Carstensen B, *et al*. Carotid intima-media thickness in individuals with and without type 2 diabetes: a reproducibility study. *Cardiovasc Diabetol* 2010;9:40.
55 Macharia M, Kengne AP, Blackhurst DM, *et al*. Indices of paraoxonase and oxidative status do not enhance the prediction of subclinical cardiovascular disease in mixed-ancestry South Africans. *Oxid Med Cell Longev* 2014;2014:135650.
56 Merlo S, Starčević JN, Mankoč S, *et al*. Vascular Endothelial Growth Factor Gene Polymorphism (rs2010963) and Its Receptor, Kinase Insert Domain-Containing Receptor Gene Polymorphism (rs2071559), and Markers of Carotid Atherosclerosis in Patients with Type 2 Diabetes Mellitus. *J Diabetes Res* 2016;2016:1482194.
57 Metcalf PA, Folsom AR, Davis CE, *et al*. Haemostasis and carotid artery wall thickness in non-insulin dependent diabetes mellitus. *Diabetes Res Clin Pract* 2000;47:25–35.
58 Meyer C, Milat F, McGrath BP, *et al*. Vascular dysfunction and autonomic neuropathy in Type 2 diabetes. *Diabet Med* 2004;21:746–51.
59 Naguib M, Ali N, ElSaraf N, *et al*. Does Serum Osteocalcin Level Affect Carotid Atherosclerosis in Post-Menopausal Diabetic Females? A Case-Control Study. *Int J Gen Med* 2022;15:4513–23.
60 Naguib M, Tarabay A, ElSaraf N, *et al*. n.d. Beclin1 circulating level as predictor of carotid intima-media thickness in patients with type 2 diabetes mellitus. *Medicine (Abingdon)*100:e26630.
61 Pan F, Xu M, Yu L, *et al*. Relationship between carotid intima-media thickness and carotid artery stiffness assessed by ultrafast ultrasound imaging in patients with type 2 diabetes. *Eur J Radiol* 2019;111:34–40.
62 Popović D, Starčević JN, Letonja MŠ, *et al*. Polymorphism rs5498 of the ICAM-1 gene affects the progression of carotid atherosclerosis in patients with type 2 diabetes mellitus. *Lipids Health Dis* 2016;15:79.
63 Sahin SB, Sahin OZ, Ayaz T, *et al*. The relationship between retinal nerve fiber layer thickness and carotid intima media thickness in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2014;106:583–9.
64 Strawbridge RJ, Hilding A, Silveira A, *et al*. Soluble CD93 Is Involved in Metabolic Dysregulation but Does Not Influence Carotid Intima-Media Thickness. *Diabetes* 2016;65:2888–99.
65 Taniwaki H, Kawagishi T, Emoto M, *et al*. Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes. Vessel wall properties in type 2 diabetes. *Diabetes Care* 1999;22:1851–7.
66 Tawfeek HM, Maghrapy HM, Elsaid FM, *et al*. Relationship between omentin-1 and carotid intima thickness in type 2 diabetes mellitus. *Egypt J Intern Med* 2014;26:68–74.
67 Uçar BMI, Çalan M, Tatar E, *et al*. Correlation of serum C1q-tumour necrosis factor-related protein 5 levels with metabolic parameters and carotid intima-media thickness in newly diagnosed type 2 diabetes mellitus patients. *Pub Online First* 2000.
68 Li X, Shen J, Lu Z, *et al*. High neutrophil-to-lymphocyte ratio is associated with increased carotid artery intima-media thickness in type 2 diabetes. *J of Diabetes Invest* 2017;8:101–7.
69 Yiu K-H, Zhao C-T, Chen Y, *et al*. Association of subclinical myocardial injury with arterial stiffness in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol* 2013;12:94.
70 Zheng T, Ge B, Liu H, *et al*. Triglyceride-mediated influence of serum angiopoietin-like protein 8 on subclinical atherosclerosis in type 2 diabetic patients: results from the GDMD study in China. *Cardiovasc Diabetol* 2018;17:84.
71 Zhang Y, Feng H, Wei Z. Association Between IL-18 and Carotid Intima-Media Thickness in Patients with Type II Diabetic Nephropathy. *Med Sci Monit* 2017;23:470–8.
72 Wang S, Wang J, Zhang R, *et al*. Association between serum haptoglobin and carotid arterial functions: usefulness of a targeted metabolomics approach. *Cardiovasc Diabetol* 2019;18:8.
73 Albu A, Fodor D, Bondor C, *et al*. Vascular risk factors in women with hypertension and diabetes mellitus type 2. *WSEAS Trans Biol Biomed* 2010;7:233–43.
74 AbdelAal AA, Abdelnabi AM. Study of Subclinical Atherosclerosis in Patients with Type 2 Diabetes Mellitus. *The Egyp J of Hosp Med* 2021;83:1203–7.
75 Areej H, Muhammad S, Farooq Y, *et al*. Carotid artery Disease Assessed by Color Doppler Flow Imaging: Comparison Between Diabetic and Non-Diabetic Patients. *Adv Life Sci* 2023;10:66–71.
76 Bakirci EM, Demirtas L, Degirmenci H, *et al*. Relationship of the total atrial conduction time to subclinical atherosclerosis, inflammation

and echocardiographic parameters in patients with type 2 diabetes mellitus. *Clinics (Sao Paulo)* 2015;70:73–80.
77 Bilgir O, Vural HA, Bilgir F, *et al*. Serum Annexin V and Anti-Annexin V levels and their relationship with metabolic parameters in patients with type 2 diabetes. *Rev Assoc Med Bras (1992)* 2019;65:1042–7.
78 Lu B, Zhao M, Jiang W, *et al*. Independent Association of Circulating Level of Chemerin With Functional and Early Morphological Vascular Changes in Newly Diagnosed Type 2 Diabetic Patients. *Medicine (Abingdon)* 2015;94:e1990.
79 Ali TM, El Askary A. The association between fetuin-A and testosterone levels and markers of arterial stiffness in Saudi subjects with type 2 diabetes mellitus. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 2018;12:1045–50.
80 Zhou Y-Y, Qiu H-M, Yang Y, *et al*. Analysis of risk factors for carotid intima-media thickness in patients with type 2 diabetes mellitus in Western China assessed by logistic regression combined with a decision tree model. *Diabetol Metab Syndr* 2020;12:8.
81 Prattichizzo F, De Nigris V, Sabbatinelli J, *et al*. CD31^{+} Extracellular Vesicles From Patients With Type 2 Diabetes Shuttle a miRNA Signature Associated With Cardiovascular Complications. *Diabetes* 2021;70:240–54.
82 Bonfigli AR, Spazzafumo L, Prattichizzo F, *et al*. Leukocyte telomere length and mortality risk in patients with type 2 diabetes. *Oncotarget* 2016;7:50835–44.
83 Kota SK, Mahapatra GB, Kota SK, *et al*. Carotid intima media thickness in type 2 diabetes mellitus with ischemic stroke. *Indian J Endocrinol Metab* 2013;17:716–22.
84 Einarson TR, Hunchuck J, Hemels M. Relationship between blood glucose and carotid intima media thickness: A meta-analysis. *Cardiovasc Diabetol* 2010;9:37.
85 Semo D, Obergassel J, Dorenkamp M, *et al*. The Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor Empagliflozin Reverses Hyperglycemia-Induced Monocyte and Endothelial Dysfunction Primarily through Glucose Transport-Independent but Redox-Dependent Mechanisms. *J Clin Med* 2023;12:1356.
86 Lontchi-Yimagou E, Sobngwi E, Matsha TE, *et al*. Diabetes mellitus and inflammation. *Curr Diab Rep* 2013;13:435–44.
87 Wolf D, Ley K. Immunity and Inflammation in Atherosclerosis. *Circ Res* 2019;124:315–27.
88 Epure AM, Anker D, Di Bernardo S, *et al*. Interventions to Decrease Carotid-Intima Media Thickness in Children and Adolescents With Type 1 Diabetes: A Systematic Review and Meta-Analysis. *Front Clin Diabetes Healthc* 2022;3:882504.
89 Chen JW, Li C, Liu ZH, *et al*. The Role of Monocyte to High-Density Lipoprotein Cholesterol Ratio in Prediction of Carotid Intima-Media Thickness in Patients With Type 2 Diabetes. *Front Endocrinol (Lausanne)* 2019;10:191.
90 Lee J, Yun JS, Ko SH. Advanced Glycation End Products and Their Effect on Vascular Complications in Type 2 Diabetes Mellitus. *Nutrients* 2022;14:3086.
91 Ho C-T, Lin C-C, Hsu H-S, *et al*. Arterial stiffness is strongly associated with insulin resistance in Chinese--a population-based study (Taichung Community Health Study, TCHS). *J Atheroscler Thromb* 2011;18:122–30.
92 Acuña L, Sanchez P, Soler L, *et al*. Total Cholesterol (Tc), Low-Density Lipoprotein Cholesterol (Ldl-C) And High-Density Lipoprotein Cholesterol (Hdl-C) Levels In Patients With Hypertension (Ht), Diabetes (Dm), Both (Ht And Dm) And Chronic Kidney Disease (Ckd). *V Health* 2015;18:A405–6.
93 Paquet S, Sassenou J, Ringa V, *et al*. Women with type 2 diabetes have LDL cholesterol levels higher than those of men, regardless of their treatment and their cardiovascular risk level. *Nutr Metab Cardiovasc Dis* 2023;33:1254–62.
94 Krane V, Winkler K, Drechsler C, *et al*. Association of LDL cholesterol and inflammation with cardiovascular events and mortality in hemodialysis patients with type 2 diabetes mellitus. *Am J Kidney Dis* 2009;54:902–11.
95 Georgieva M, Xenodochidis C, Krasteva N. Old age as a risk factor for liver diseases: Modern therapeutic approaches. *Exp Gerontol* 2023;184:112334.
96 Rosada A, Kassner U, Weidemann F, *et al*. Hyperlipidemias in elderly patients: results from the Berlin Aging Study II (BASEII), a cross-sectional study. *Lipids Health Dis* 2020;19:92.
97 Inaraja V, Thuissard I, Andreu-Vazquez C, *et al*. Lipid profile changes during the menopausal transition. *Menopause* 2020;27:780–7.
98 Ivanova EA, Myasoedova VA, Melnichenko AA, *et al*. Small Dense Low-Density Lipoprotein as Biomarker for Atherosclerotic Diseases. *Oxid Med Cell Longev* 2017;2017.
99 Al Mansour MA. The Prevalence and Risk Factors of Type 2 Diabetes Mellitus (DMT2) in a Semi-Urban Saudi Population. *IJERPH* 2020;17:7.
100 Jung E, Kong SY, Ro YS, *et al*. Serum Cholesterol Levels and Risk of Cardiovascular Death: A Systematic Review and a Dose-Response Meta-Analysis of Prospective Cohort Studies. *IJERPH* 2022;19:8272.
101 Hong S, Han K, Park CY. The triglyceride glucose index is a simple and low-cost marker associated with atherosclerotic cardiovascular disease: a population-based study. *BMC Med* 2020;18:361.
102 Otero YF, Stafford JM, McGuinness OP. Pathway-selective insulin resistance and metabolic disease: the importance of nutrient flux. *J Biol Chem* 2014;289:20462–9.
103 Schofield JD, Liu Y, Rao-Balakrishna P, *et al*. Diabetes Dyslipidemia. *Diabetes Ther* 2016;7:203–19.
104 Nordestgaard LT, Christoffersen M, Afzal S, *et al*. Triglycerides as a Shared Risk Factor between Dementia and Atherosclerotic Cardiovascular Disease: A Study of 125 727 Individuals. *Clin Chem* 2021;67:245–55.
105 Agbaje AO, Barker AR, Mitchell GF, *et al*. Effect of Arterial Stiffness and Carotid Intima-Media Thickness Progression on the Risk of Dysglycemia, Insulin Resistance, and Dyslipidemia: a Temporal Causal Longitudinal Study. *Hypertension* 2022;79:667–78.
106 Farbstein D, Levy AP. HDL dysfunction in diabetes: causes and possible treatments. *Expert Rev Cardiovasc Ther* 2012;10:353–61.
107 Van Linthout S, Spillmann F, Schultheiss H-P, *et al*. High-density lipoprotein at the interface of type 2 diabetes mellitus and cardiovascular disorders. *Curr Pharm Des* 2010;16:1504–16.
108 Ormazabal V, Nair S, Elfeky O, *et al*. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol* 2018;17:122.
109 Haase KR, Sattar S, Pilleron S, *et al*. A scoping review of ageism towards older adults in cancer care. *J Geriatr Oncol* 2023;14:101385.