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2型糖尿病与钙化性主动脉瓣疾病的中介变量分析

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摘 要

本研究探讨在T2DM与CAVD的关系中体重指数、高血压、慢性肾脏病、甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值的中介作用。纳入2018年1月至2022年12月青岛大学附属医院心脏大血管外科和健康体检中心的患者数据，采用因果中介效应分析方法，探讨T2DM与CAVD的中介变量。共纳入3979名参与者，CAVD组1925人，非CAVD组2054人。高血压、甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值、慢性肾脏病的中介效应分别为0.114、0.042、0.029、0.015、0.006 (P均<0.001)。高血压的中介效应最大，其次是甘油三酯葡萄糖指数。在糖尿病患者中，强化管理血压、血糖和血脂可降低CAVD风险。

关键词

糖尿病，钙化性主动脉瓣疾病，高血压，甘油三酯葡萄糖指数，中介效应分析

Analysis of Mediator Variables of Type 2 Diabetes and Calcific Aortic Valve Disease

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Abstract

This study aims to investigate the mediating effects of body mass index, hypertension, chronic

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kidney disease, triglyceride-glucose index, total cholesterol/high-density lipoprotein ratio, and neutrophil-to-lymphocyte ratio in the relationship between type 2 diabetes mellitus (T2DM) and calcific aortic valve disease (CAVD). Data from patients at the Department of Cardiothoracic Surgery and the Health Examination Center of Qingdao University Affiliated Hospital between January 2018 and December 2022 were included. Causal mediation analysis was used to explore the mediating variables in the association between T2DM and CAVD. A total of 3979 participants were included, with 1925 in the CAVD group and 2054 in the non-CAVD group. The mediating effects of hypertension, triglyceride-glucose index, total cholesterol/high-density lipoprotein ratio, neutrophil-to-lymphocyte ratio, and chronic kidney disease were 0.114, 0.042, 0.029, 0.015, and 0.006, respectively (all P < 0.001). Hypertension had the largest mediating effect, followed by the triglyceride-glucose index. Based on these findings, intensive management of blood pressure, blood glucose, and blood lipids in diabetic patients may reduce the risk of CAVD.

Keywords

Diabetes Mellitus, Calcific Aortic Valve Disease, Hypertension, Triglyceride-Glucose Index, Analysis of Mediation Effects

1. 引言

钙化性主动脉瓣疾病(calcific aortic valve disease, CAVD)的发病率随着人群年龄的增长而增加，在 60 岁以上人群中的发病率为 2% [1]。CAVD 导致的主动脉瓣膜钙化可导致患者出现主动脉瓣狭窄，随着狭窄加重，患者可出现心力衰竭、晕厥和心绞痛等严重的并发症[2]-[5]。当 CAVD 患者出现症状后，如果不及时进行主动脉瓣治疗，患者的 2 年死亡率超过 50% [6]。随着全球老龄化加重，CAVD 的患病人数预计将从 2000 年的 250 万增加到 2030 年的 450 万[7]。CAVD 是一种多因素疾病[4]。多项研究证实 T2DM 是 CAVD 的独立危险因素[8]-[10]。T2DM 导致患者出现主动脉瓣钙化的病理机制复杂，通过炎症反应、氧化应激、内皮细胞功能障碍等影响患者的瓣膜，进而出现主动脉瓣钙化[11]-[13]。但 T2DM 如何诱导患者发生 CAVD 的机制仍有待进一步验证[10]。当前 CAVD 和 T2DM 都已成为全球老龄化的社会健康负担[14]-[16]，深入了解这两种疾病的关联，有助于临床医生监控 T2DM 患者 CAVD 的发生。目前没有研究 T2DM 与 CAVD 之间的中介变量。本研究通过回顾性地探究 T2DM 与 CAVD 之间的中介变量，为临床上 T2DM 患者预防和治疗 CAVD 提供新思路。

2. 对象与方法

2.1. 研究对象

病例组是 2018 年 1 月~2022 年 12 月就诊于青岛大学附属医院心脏大血管外科的患者，且超声心动图的检查结果诊断为钙化性主动脉瓣疾病。对照组是就诊于青岛大学附属医院体检中心的人群，且超声心动图的检查无心脏瓣膜病变。本研究在青岛大学附属医院开展，研究方案已通过青岛大学附属医院医学伦理委员会的审批(伦理批号：QYFYWZLL28076)，同时免除患者签署知情同意书。患者入组及分组流程详见图 1。

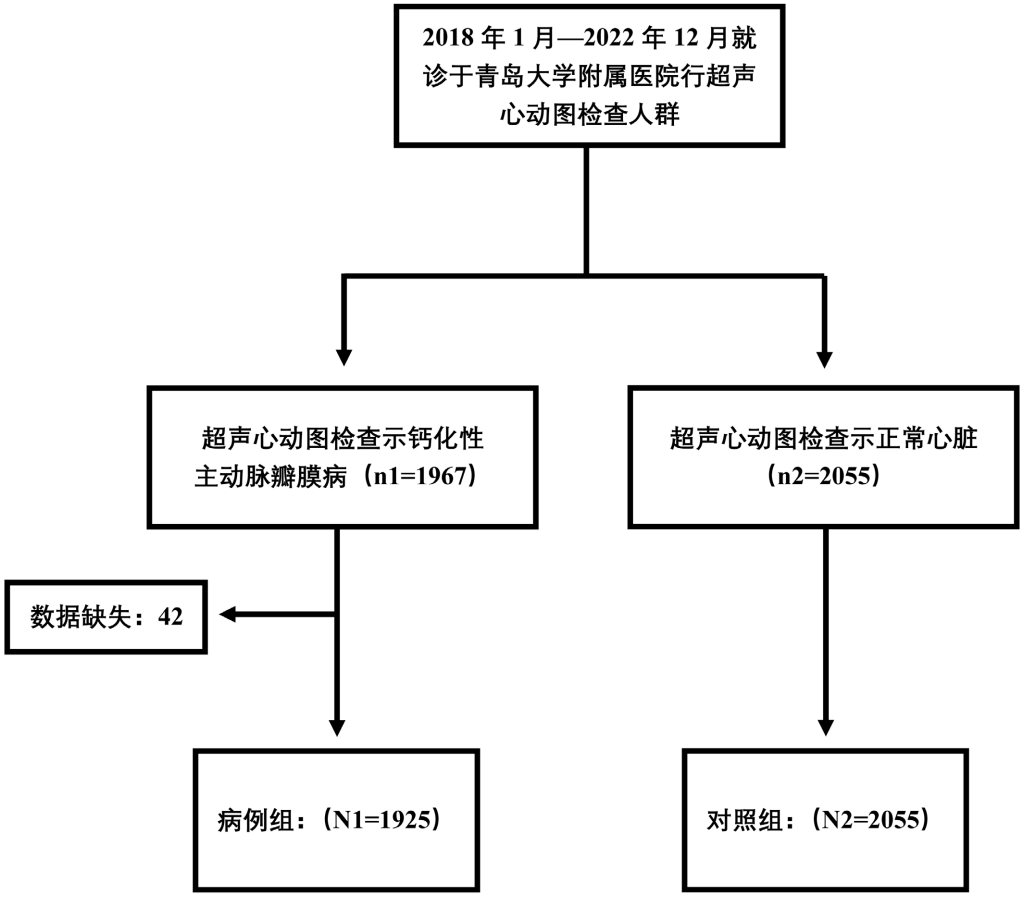


Figure 1. Flowchart of participant enrollment
图 1. 研究对象入组流程图

2.2. 围手术期管理

病例组均进行冠状动脉搭桥手术，使用相同的麻醉药物及外科技术。手术后密切观察患者的生命体征。

2.3. 诊断与定义

CAVD：超声心动图符合 2020 年 AHA/ACC 和 2021 年 ESC/EACTS 瓣膜性心脏病管理指南中主动脉瓣钙化的诊断标准，主动脉瓣钙化(主动脉瓣增厚超过 3 mm 以上)、回声增强、瓣叶变硬、活动受限[17]-[20]。T2DM：患者的空腹血糖 ≥ 7.8 mmol/L 或一天中任何时间血糖 ≥ 11.1 mmol/L 或空腹血糖 < 7.8 mmol/L，但口服 75%葡萄糖耐量试验二小时血糖 ≥11.1 mmol/L；或者患者的糖化血红蛋白 >6.5 mmol/L；或者患者已经被诊断糖尿病，目前使用运动和饮食方案控制血糖，或接受降血糖药物的治疗[21]。高血压：当连续 3 次，非同日测量 SBP ≥ 130 mmHg 或 DBP ≥ 80 mmHg，或者已接受降压治疗的患者[22]。慢性肾脏病：患者出现>3 个月肾小球滤过率[estimated glomerular filtration rate (eGFR)] < 60 mL/min/1.73 m^2 [23]。eGFR: Chronic Kidney Disease Epidemiology Collaboration (慢性肾脏病-EPI) equation: eGFR = $\alpha \times (Scr/\beta)^{\gamma \times 0.993^{age}}$, if patient is female: $\alpha = 144$, $\beta = 62$, $\gamma = -0.329$ (Scr ≤ 62 umol/L) or −1.209 (Scr > 62 umol/L); if patient is male: $\alpha = 141$, $\beta = 80$, $\gamma = -0.411$ (Scr ≤ 80 umol/L) or −1.209 (Scr > 80 umol/L) [24]。

甘油三酯－葡萄糖指数：Ln[Triglyceride(mg/dl) × Glucose(mg/dl) mmol/L/2] = Ln[Triglyceride(mmol/L) × 88.6 × Glucose(mmol/L) × 18/2] [25]。

2.4. 统计分析

缺失数据超过 10%的变量被排除在分析之外，而缺失数据少于 10%的变量则使用 R 语言 4.2.3 进行多重插补进行插补，以确保无偏估计。使用 IBM SPSS 26.0 进行数据正态性检验，研究对象正态分布的计量资料以均数 ± 标准差($\bar{x} \pm s$)表示，非正态分布的计量资料以中位数(第 25，75 百分位数)表示。本研究使用了 Student's t-test 或 Mann-Whitney U-test 比较组间的差异，计数资料以例(百分比)表示，并通过 Pearson chi-square test 或 Fisher exact test 进行比较。本研究进行因果中介分析时通过 R 语言采用 Bootstrap 法(T = 1000 次)进行(图 2 为中介图示)，探究 T2DM (自变量)与 CAVD (因变量)的中介变量，量化中介效应的大小。采用双尾检验，P 值 ＜0.05 被认为具有统计学显著性差异。

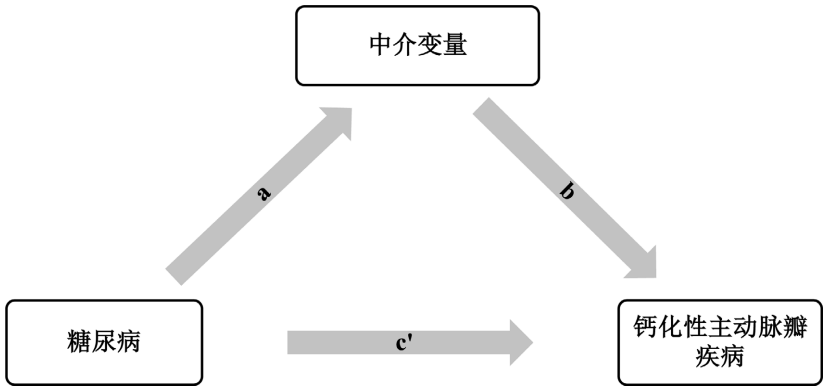


Figure 2. Illustration of mediation effects
图 2. 中介效应图示

3. 结果

共 3979 名研究对象入组，根据研究对象是否患有 CAVD 进行分组，分为病例组(CAVD 组) 1925 例与对照组(non-CAVD 组) 2054 例。两组研究对象的基线特征见表 1。

Table 1. Baseline characteristics of study participants
表 1. 研究对象基线信息

研究指标	CAVD (N1 = 1925)	non-CAVD (N2 = 2054)	P-value
人口学特征			
性别			<0.001
男性	1404 (72.9)	1199 (58.4)	
年龄，years	63.8 (8.4)	57.4 (11.8)	<0.001
身高，cm	166.9 (7.6)	166.3 (8.7)	0.019
体重，kg	71.7 (11.9)	71.3 (13.0)	0.292
体重指数，kg/m^2	25.7 (3.2)	25.7 (3.5)	0.943
收缩压，mmHg	125.6 (16.7)	130.7 (18.8)	<0.001
舒张压，mmHg	71.9 (10.6)	79.9 (11.8)	<0.001
既往史			
吸烟史	846 (43.9)	434 (21.1)	<0.001
饮酒史	560 (29.1)	494 (24.1)	<0.001

续表

用药史			
2 型糖尿病	961 (49.9)	305 (14.8)	<0.001
高血压	1547 (80.4)	611 (29.7)	<0.001
慢性肾脏病	181 (9.4)	63 (3.1)	<0.001
实验室检查			
血肌酐，μmol/L	78.0 (24.5)	75.4 (13.9)	<0.001
甘油三酯，mmol/L	1.4 [1.1, 2.0]	1.2 [0.8, 1.8]	<0.001
总胆固醇，mmol/L	4.4 (0.9)	5.3 (0.9)	<0.001
高密度脂蛋白，mmol/L	1.2 (0.3)	1.6 (0.4)	<0.001
低密度脂蛋白，mmol/L	2.6 (0.9)	3.0 (0.8)	<0.001
空腹血糖，mmol/L	5.6 [4.9, 6.7]	5.1 [4.7, 5.6]	<0.001
尿酸，μmol/L	335.8 (90.4)	333.9 (86.4)	0.498
血红蛋白，g/L	131.8 (16.0)	146.5 (15.4)	<0.001
中性粒细胞计数，10^9/L	3.9 [3.1, 4.6]	3.2 [2.6, 3.9]	<0.001
淋巴细胞计数，10^9/L	1.9 (0.6)	2.0 (0.6)	<0.001
血小板计数，10^9/L	218.7 (59.7)	227.4 (51.1)	<0.001
eGFR, ml/min/1.73m^2	85.0 (18.3)	89.2 (13.8)	0.001
中性粒细胞/淋巴细胞比值	2.1 [1.6, 2.5]	1.6 [1.3, 2.1]	<0.001
甘油三酯葡萄糖指数	8.9 (0.6)	8.5 (0.7)	<0.001
总胆固醇/高密度脂蛋白比值	4.0 (0.9)	3.4 (0.8)	<0.001

在未调整混杂变量时，患者的 T2DM 与 CAVD 之间存在显著的关联 OR = 5.717 [95% CI (4.916~6.648), P-value < 0.001] (表 2)。逐步调整患者的混杂因素(年龄、性别、吸烟史和饮酒史)后 T2DM 与 CAVD 之间一直存在显著的相关性(P < 0.001)，证明 T2DM 和 CAVD 之间的中介分析的途径 c’成立。当纳入假定中介变量(高血压、甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值、慢性肾脏病和体重指数)后会影响 T2DM 与 CAVD 的 OR 值，证明在 T2DM 与 CAVD 之间存在中介途径。

通过 ROC 曲线可直观地表现假定中介变量与 T2DM 之间的联系，其中甘油三酯葡萄糖指数的诊断价值最好(AUC = 0.690) (图 3(a))。

Table 2. Relationship between Type 2 Diabetes Mellitus (T2DM) and Calcific Aortic Valve Disease (CAVD)
表 2. T2DM 与 CAVD 关系

	OR (95% CI)	P-value
Model 1	5.717 (4.916, 6.648)	<0.001
Model 2	4.975 (4.252, 5.822)	<0.001
Model 3	5.014 (4.272, 5.885)	<0.001
Model 4	3.401 (2.861, 4.043)	<0.001
Model 5	4.059 (3.440, 4.789)	<0.001
Model 6	4.618 (3.921, 5.438)	<0.001
Model 7	1.876 (1.699, 2.072)	<0.001

续表

Model 8	4.897 (4.170, 5.751)	<0.001
Model 9	5.063 (4.310, 5.947)	<0.001
Model 10	2.826 (2.342, 3.409)	<0.001

Model 1 未调整；Model 2 调整 age，gender；Model 3 调整 age，gender，smoke，alcohol；Model 4 调整 Model3 + HTN；Model 5 调整 Model3 + TyG；Model 6 调整 Model3 + TC/HDL；Model 7 调整 Model3 + NLR；Model 8 调整 Model3 + CKD；Model 9 调整 Model3 + BMI；Model 10 调 Model3 + HTN，TyG，TC/HDL，NLR，CKD and BMI。

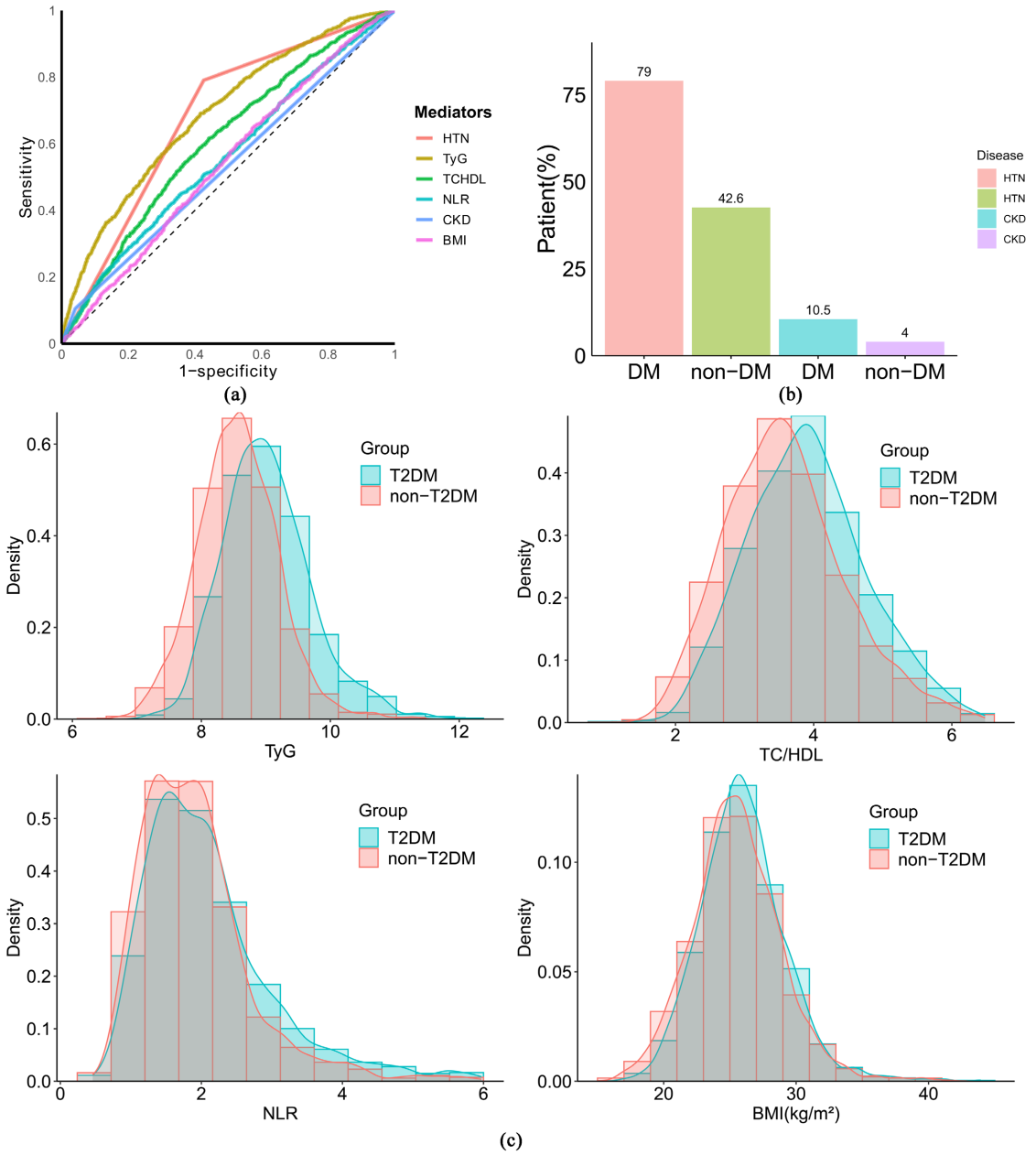


Figure 3. The relationship diagram of diabetes with hypertension, triglyceride glucose index, total cholesterol/high-density lipoprotein ratio, neutrophil/lymphocyte ratio, chronic kidney disease, and body mass index

图 3. 糖尿病与高血压、甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值、慢性肾脏病和体重指数的关系图

通过条形图观察到 T2DM 和 non-T2DM 两组间的高血压和慢性肾脏病发病率存在明显的差异(图3(b))，通过柱状图可观察到 T2DM 与甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值和体重指数之间也存在明显的差异(图 3(c))。进一步多元回归分析，充分调整混杂变量(年龄、性别、吸烟史和饮酒史)后显示 T2DM 与甘油三酯葡萄糖指数存在正相关性 $\beta = 0.307$ [95% CI (0.405~0.493), P-value < 0.001]；T2DM 与总胆固醇/高密度脂蛋白比值存在正相关性 $\beta = 0.264$ [95% CI (0.206~0.322), P-value < 0.001]；T2DM 与中性粒细胞/淋巴细胞比值存在正相关性 $\beta = 0.143$ [95% CI (0.086~0.199), P-value < 0.001]；T2DM 与体重指数存在正相关性 $\beta = 0.555$ [95% CI (0.329~0.781), P-value < 0.001] (表 3(a))，同时，在充分调整混杂变量后的多元逻辑回归显示 T2DM 与高血压存在显著相关性 OR = 4.248 [95% CI (3.618~4.989), P-value < 0.001]；T2DM 与慢性肾脏病存在显著相关性 OR = 2.228 [95% CI (1.703~2.916), P-value < 0.001] (表 3(b))。

Table 3. (a) Relationship between DM and TyG, TC/HDL, NLR and BMI; (b) Relationship between DM and HTN, CKD
表 3. (a) 糖尿病与甘油三酯葡萄糖指数(TyG)、总胆固醇/高密度脂蛋白比值(TC/HDL)、中性粒细胞/淋巴细胞比值(NLR)和体重指数(BMI)的关系；(b) 糖尿病与高血压(HTN)和慢性肾脏病(CKD)的关系

(a)		
Mediator	**RR (95% CI)**	**P-value**
TyG	0.307(0.405, 0.493)	<0.001
TC/HDL	0.264(0.206, 0.322)	<0.001
NLR	0.143(0.086, 0.199)	<0.001
BMI	0.555(0.329, 0.781)	<0.001
(b)		
Mediator	**OR (95% CI)**	**P-value**
HTN	4.248 (3.618, 4.989)	<0.001
CKD	2.228 (1.703, 2.916)	<0.001

Adjusting variables: age, gender, smoke, alcohol.

通过 ROC 曲线展现假定中介变量对于 CAVD 诊断价值(图 4)，高血压对于 CAVD 的诊断价值最好(AUC = 0.753)。通过条形状图展现出高血压/non-高血压或慢性肾脏病/non-慢性肾脏病的 CAVD 发病率间存在明显的差异(图 4(b))。使用限制性立方样图(Restricted cubic spline, RCS)，利用平滑曲线拟合直观反映假定中介变量甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值和体重指数与 CAVD OR 之间的关系(图 4(c))，随着甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值和中性粒细胞/淋巴细胞比值升高 CAVD 发生的风险逐渐升高，本研究发现甘油三酯葡萄糖指数 > 8.8、总胆固醇/高密度脂蛋白比值 > 4、中性粒细胞/淋巴细胞比值 > 3 时 CAVD OR > 1，随着体重指数的升高 CAVD 发生风险先逐渐升高，再逐渐降低，呈现倒 U 型，然而通过 RCS 可以发现体重指数其结果不具有统计学意义。通过逻辑回归分析假定中介变量与 CAVD 的关系(表 4)，在充分调节混杂变量后显示高血压、甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值和慢性肾脏病与 CAVD 存在显著的相关性(P-value < 0.05)，但体重指数与 CAVD 并未出现相关性。上述分析说明只有高血压、甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值和慢性肾脏病满足中介途径 b。

将满足中介分析前提条件的假定中介变量纳入中介分析，进一步的中介效应统计分析后发现高血压、甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值和慢性肾脏病在 T2DM 与

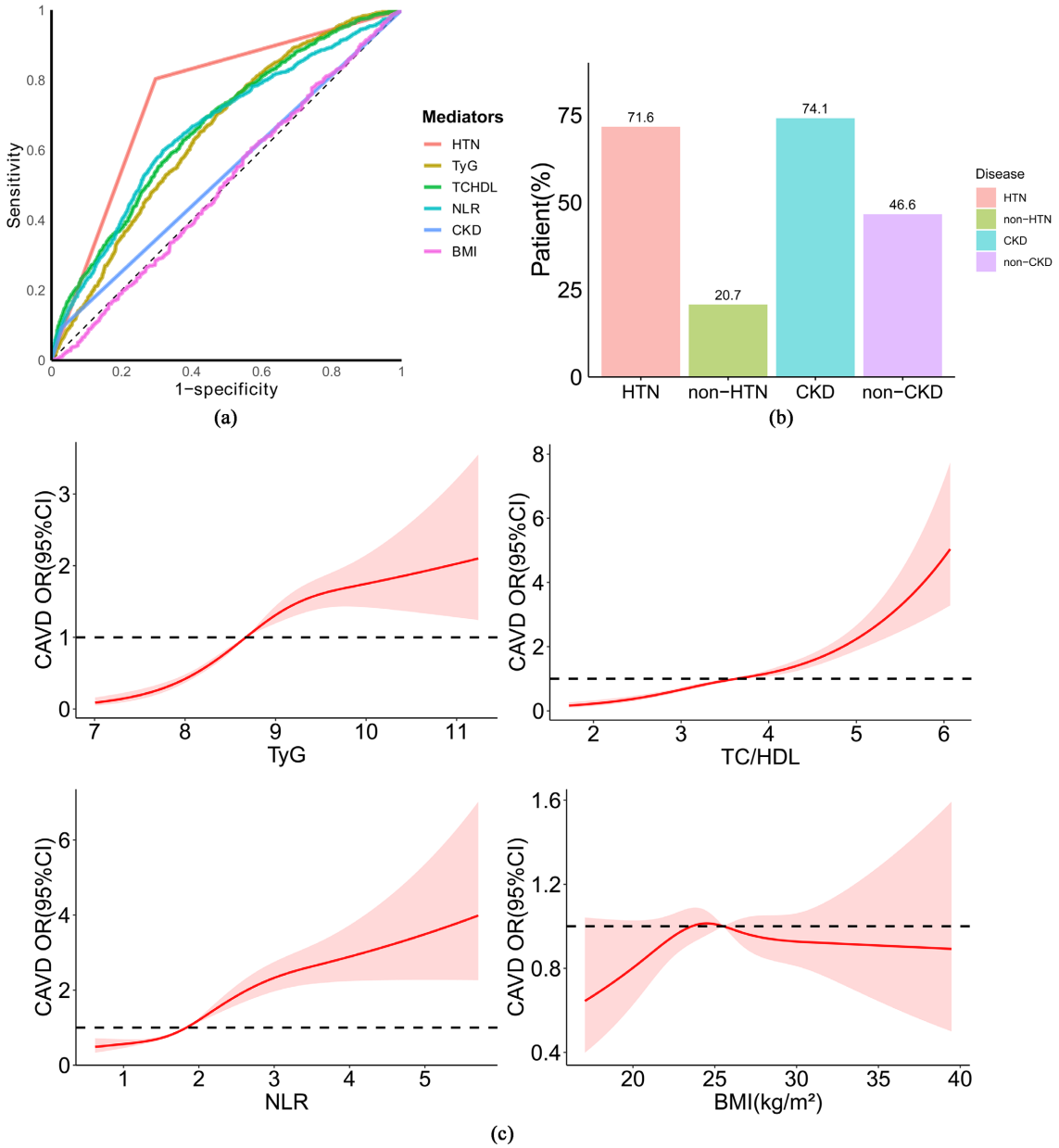


Figure 4. The relationship diagram of hypertension, triglyceride glucose index (TyG), total cholesterol/high-density lipoprotein ratio (TC/HDL), neutrophil-to-lymphocyte ratio (NLR), chronic kidney disease (CKD), and body mass index (BMI) with calcific aortic valve disease (CAVD)

图 4. 高血压、甘油三酯葡萄糖指数(TyG)、总胆固醇/高密度脂蛋白比值(TC/HDL)、中性粒细胞/淋巴细胞比值(NLR)、慢性肾脏病(CKD)和体重指数(BMI)与钙化性主动脉瓣疾病(CAVD)的关系图

Table 4. Hypothetical relationships between mediator variables and Calcific Aortic Valve Disease (CAVD)

表 4. 假定中介变量与 CAVD 的关系

	OR (95% CI)	P-value
DM	5.014 (4.272, 5.885)	<0.001
HTN	8.376 (7.149, 9.813)	<0.001
TyG	2.220 (1.986, 2.483)	<0.001

续表

TC/HDL	1.955 (1.793, 2.132)	<0.001
NLR	1.866 (1.699, 2.050)	<0.001
CKD	2.519 (1.839, 3.450)	<0.001
BMI	1.004 (0.983, 1.025)	0.741

调整 age, gender, smoke, alcohol.

CAVD 之间表现出显著统计学意义，中介占比的 P-value < 0.001，中介占比分别为 34.1%、12.7%、8.6%、4.5%和 1.8% (表 5)，并且甘油三酯葡萄糖指数和高血压在其中介过程中占比最高，进一步使用森林图直观地展示各变量的中介占比(图 5)，最后根据上述结果绘制的中介效应图(图 6)。

Table 5. Mediation analysis results of Type 2 Diabetes Mellitus (T2DM) and Calcific Aortic Valve Disease (CAVD)
表 5. T2DM 和 CAVD 中介分析结果

Mediator	Total effect	Mediation effect	Direct effect	PM (%)	P-value of PM
HTN	0.335 (0.302, 0.370)	0.114 (0.100, 0.130)	0.220 (0.186, 0.250)	34.1	<0.001
TyG	0.335 (0.302, 0.370)	0.042 (0.033, 0.050)	0.292 (0.258, 0.320)	12.7	<0.001
TC/HDL	0.335 (0.302, 0.370)	0.029 (0.022, 0.040)	0.306 (0.273, 0.340)	8.6	<0.001
NLR	0.335 (0.302, 0.370)	0.015 (0.008, 0.020)	0.319 (0.288, 0.350)	4.5	<0.001
CKD	0.335 (0.302, 0.370)	0.006 (0.003, 0.010)	0.328 (0.296, 0.360)	1.8	<0.001
BMI	0.335 (0.302, 0.370)	−0.002 (−0.005, 0.000)	0.336 (0.304, 0.370)	−0.6	0.110

调整 age, gender, smoke, alcohol; PM: proportion mediate.

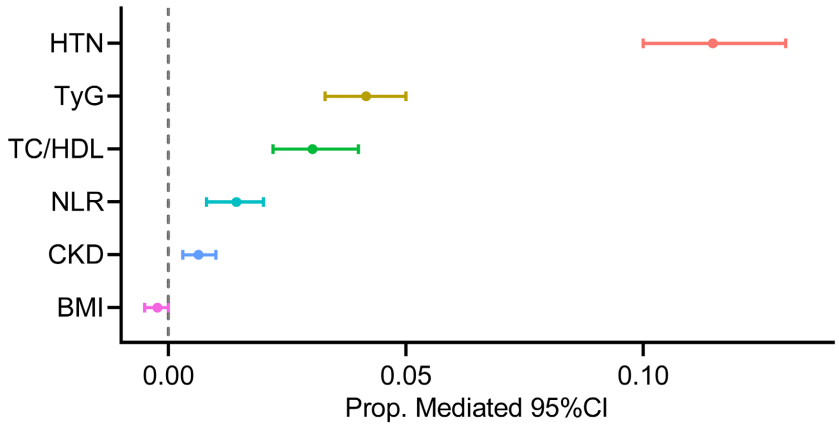
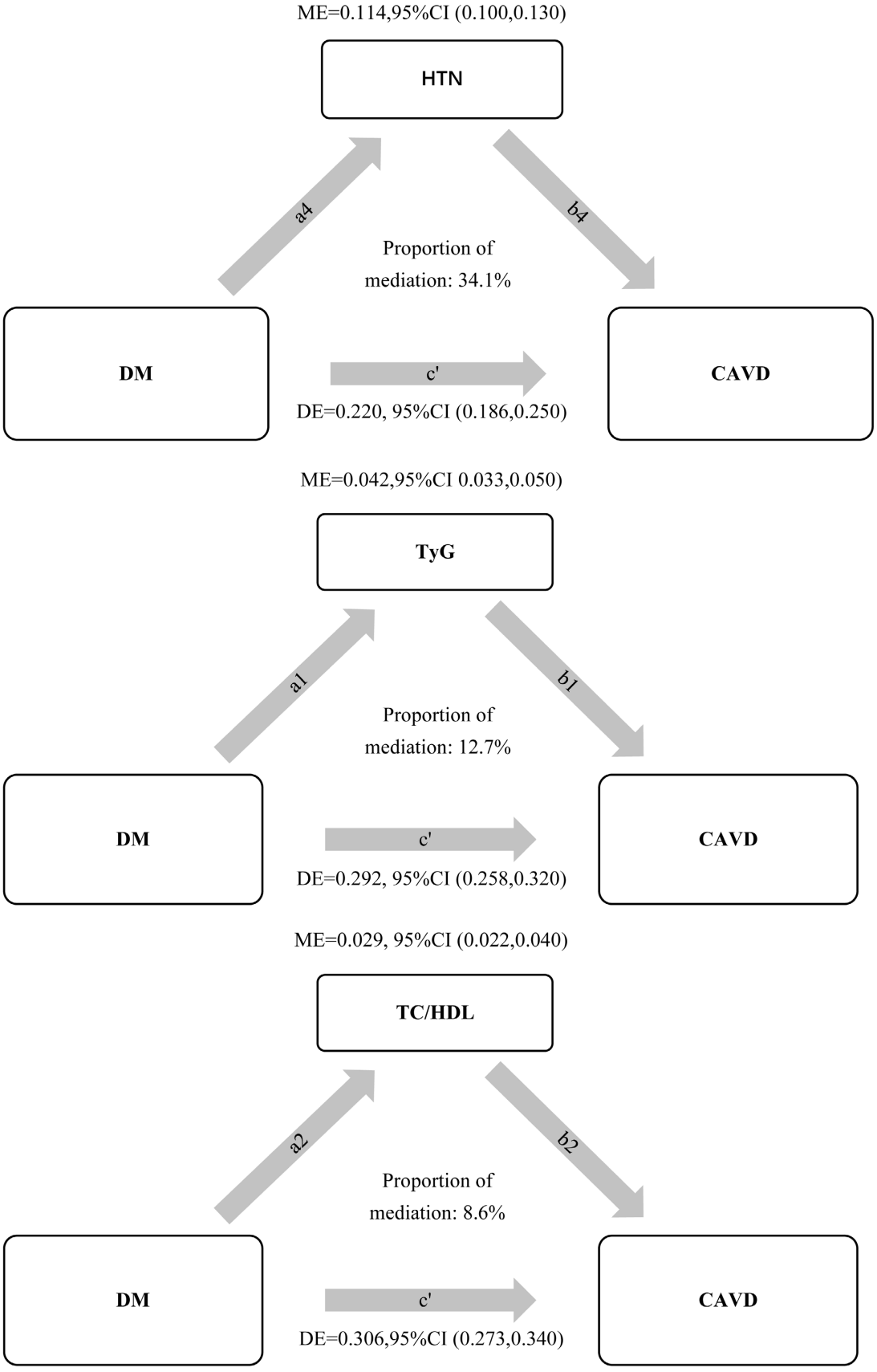
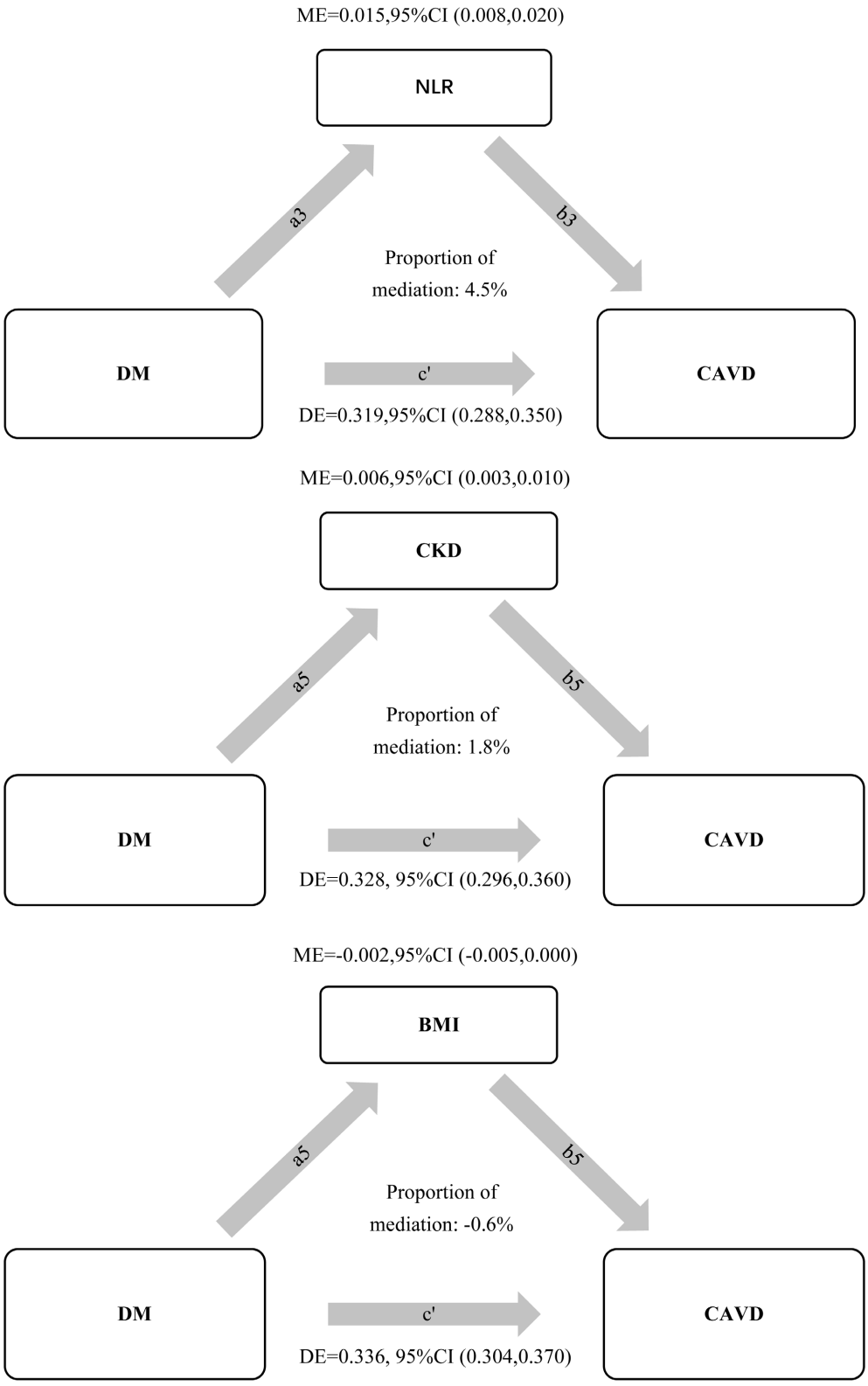


Figure 5. Indirect effects (with 95% CIs) from the Bootstrap samples
图 5. 来自自助抽样(Bootstrap)的间接效应(附 95%置信区间)

4. 讨论

本研究基于 3979 名研究对象进行中介效应分析，在 CAVD 中，首次证实了高血压、甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值和慢性肾脏病为 T2DM 与 CAVD 之间的中介变量(P-value of PM < 0.05)，中介占比分别为 34.1%、12.7%、8.6%、4.5%和 1.8% (P-value of PM < 0.05)。


ME=0.114,95%CI (0.100,0.130)
HTN
a4
b4
Proportion of
mediation: 34.1%
DM
c'
CAVD
DE=0.220, 95%CI (0.186,0.250)
ME=0.042,95%CI 0.033,0.050)
TyG
a1
b1
Proportion of
mediation: 12.7%
DM
c'
CAVD
DE=0.292, 95%CI (0.258,0.320)
ME=0.029, 95%CI (0.022,0.040)
TC/HDL
a2
b2
Proportion of
mediation: 8.6%
DM
c'
CAVD
DE=0.306,95%CI (0.273,0.340)



调整 age, gender, smoke, alcohol; ME: Mediation effect; DE: Direct effect.

Figure 6. Mediation models of the relationship between DM and CAVD
图 6. 糖尿病与钙化性主动脉瓣疾病(CAVD)关系的中介模型

CAVD 已经成为心脏瓣膜疾病中最常见的疾病，随着全球老龄化加重，CAVD 的发病人数会进一步增加，除了手术治疗外，尚无有效的药物可以治疗 CAVD [26]-[28]，临床研究已经表明了 T2DM 是 CAVD 的独立危险因素，并且 T2DM 可以加速 CAVD 的发生和进展[9] [10] [29]-[31]。深入探究 CAVD 合并 T2DM 的发病机制以及解密这两种常见慢性疾病之间的关联，有助于我们找到有效的预防和治疗方法，降低 T2DM 患者发生 CAVD，改善 CAVD 合并 T2DM 患者的预后[10]。但当前对于 T2DM 与 CAVD 之间的中介变量尚无研究探讨。

在 2017 年 YAN AT 等人进行了一项 13 年，112 万人的多中心观察性研究指出高血压是 CAVD 的危险因素(HR: 1.71; 95% CI: 1.66~1.76) [29]。CAVD 和动脉粥样硬化早期阶段的相似性，医生常采用血管紧张素转换酶抑制剂(ACEI)和他汀类药物在 CAVD 的治疗中使用，一项回顾性研究结果表明血 ACEI 对预防主动脉瓣膜钙化产生一定的治疗作用[32] [33]，印证了高血压与 CAVD 之间存在一定的关联。本研究证实高血压是 T2DM 与 CAVD 之间的中介变量，高血压的中介占比最高。对于 T2DM 和 CAVD 之间通过高血压介导的机制尚无直接研究，可能与 T2DM 激活患者的全身肾素－血管紧张素－醛固酮系统，并与血管阻力和动脉压增加相关，导致 T2DM 患者出现血压的升高，血管硬化和相关的心血管疾病[34] [35]，当 T2DM 患者出现高血压以后，血流动力学变化可直接损害 VECs 的结构和功能导致炎症浸润和氧化应激，导致患者的主动脉瓣瓣膜出现钙化，从而促进 CAVD 的发生和进展[27]。T2DM 导致 CAVD 的过程中，高血压表现出中介作用(P-value of PM < 0.01)，建议在临床上对于 T2DM 患者应该及早关注患者的血压情况，早期监控患者血压，控制在合理范围内，有利于降低 CAVD 的发生风险。

本研究证实甘油三酯葡萄糖指数为 T2DM 与 CAVD 的中介变量，中介占比为 12.7%。对于 T2DM 和 CAVD 之间通过甘油三酯葡萄糖指数介导的机制也尚无直接研究。GUERRERO-ROMERO F 等人在 2010 年进行的一项横断面研究，明确指出了甘油三酯葡萄糖指数是评估胰岛素抵抗(IR)的最佳工具(敏感度：96.5%；特异性：85.0%) [36]，可能与 T2DM 导致患者出现高胰岛素血症有关，当前临床研究已将甘油三酯葡萄糖指数作为反应了 T2DM 患者高胰岛素血症水平的简便指标[36]-[38]，同时，研究指出甘油三酯葡萄糖指数指与心血管疾病的发生和预后相关[39]。高胰岛素血症减弱了患者的血管舒张作用，影响患者的血管系统功能，导致瓣膜内皮细胞的功能障碍，损害 T2DM 患者的主动脉瓣中 VECs 的功能而诱发主动脉瓣钙化[40] [41]，对预防 CAVD 的 T2DM 患者中同时应早期管理甘油三酯葡萄糖指数指标，将其控制在合理范围内，降低 CAVD 发生的风险。

本研究证实总胆固醇/高密度脂蛋白比值为 T2DM 与 CAVD 的中介变量，中介占比为 8.6%。T2DM 和 CAVD 之间通过总胆固醇/高密度脂蛋白比值介导的机制无直接研究。结合当前对于总胆固醇/高密度脂蛋白比值的研究，推测 T2DM 和总胆固醇/高密度脂蛋白比值与 CAVD 之间的联系，可能与 T2DM 导致患者机体出现血脂水平紊乱后，引发强烈的炎症反应有关。一项针对中国受试者的多项研究表明总胆固醇/高密度脂蛋白比值与 IR 存在显著相关性 AUC = 0.770 [42]，结合 IR 机制最终导致胆固醇晶体出现在 VECs、VICs 和巨噬细胞衍生的泡沫细胞中，在瓣膜上形成广泛的钙化[43]。早期的研究中已经证实在心血管疾病预测方面，总胆固醇/高密度脂蛋白比值是能反应机体血脂水平的指标[44]，对预防 CAVD 的 T2DM 患者在关注甘油三酯葡萄糖指数的同时，也应关注总胆固醇/高密度脂蛋白比值指标，降低患者发生 CAVD 的风险。

中性粒细胞/淋巴细胞比值已成为全身炎症反应的常规标志物[45] [46]。本研究结果证实中性粒细胞/淋巴细胞比值为 T2DM 与 CAVD 的中介变量。对于 T2DM 和 CAVD 之间通过中性粒细胞/淋巴细胞比值介导的机制尚无直接研究，结合当前对于中性粒细胞/淋巴细胞比值的研究，以及 T2DM 和 CAVD 之间的联系，T2DM 可导致患者的机体出现炎症反应，通过影响机体炎症水平和脂质代谢的相互作用，导致 CAVD 发生[7]，在预防 CAVD 的 T2DM 患者可以关注其中性粒细胞/淋巴细胞比值指标，及时进行有针

对的治疗，降低发生 CAVD 的风险。

慢性肾脏病为 T2DM 与 CAVD 之间的中介变量。对于 T2DM 和 CAVD 之间通过慢性肾脏病介导的机制尚无直接研究。T2DM 导致患者机体出现的高血糖环境会直接损伤患者的肾脏，导致患者糖尿病肾病的发生[47]。早期肾脏功能受到影响后，患者的肾小球滤过功能会受到损伤，出现肾小球的滤过率下降，内皮细胞窗孔缩小等，进而出现缩孔综合征(shrunken pore syndrome, SPS)，当出现患者发生 SPS 后，SPS 导致患者的肾小球滤过率降低，从而血液中胱抑素 C、β2-MG、RBP 等这些相对分子质量为 10~30,000 的蛋白积聚，影响了中性粒细胞的迁移，导致局部炎症反应的出现[48]。Almen M S 等人与 Xhakollari L 等人的研究团队通过对 SPS 患者的蛋白质组学研究发现，SPS 患者体内 MCP-3、IL-6、MCP-1、IL-18 等促进动脉粥样硬化的蛋白增多，当这些蛋白在患者的血液中积聚，进一步造成机体慢性炎症状态，同时促进了动脉粥样硬化的形成[49] [50]。随着疾病进展当患者出现慢性肾脏病后，进一步加剧了患者 CAVD 的发生[51] [52]。在本研究结果中发现 T2DM 导致 CAVD 的过程中，慢性肾脏病扮演了中介变量角色(P-value of PM < 0.05)。

本研究发现体重指数不能满足中介分析的假定条件。在柳叶刀糖尿病内分泌杂志发表的综述中指出体重指数与心血管疾病存在显著的相关性[53]。一项全国 150 万人的研究指出，体重指数会影响 T2DM 患者的心血管事件发生率(例如：心肌梗死、缺血性卒中、心房颤动、心力衰竭) [54]。但上述研究的结局中并未明确指出 CAVD，因此上述结论对于 CAVD 的临床实践有待进一步探究。

本研究也存在一些不足：首先，本研究为单中心回顾性研究且样本量较小，结果可能存在一定的偏倚；其次，本研究中有 1.0% (42/4021)研究对象的数据由于严重缺失，无法进行统计学插补，最终被剔除了本研究，可能造成潜在的偏移。

对比既往研究中对于 CAVD 的探索，本研究首次证实了 T2DM 可通过变量高血压、甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值和慢性肾脏病的中介途径，参与调节 CAVD，在队列中，高血压的中介效应最大，其次为甘油三酯葡萄糖指数。基于本研究的结果，对于以后的临床工作，我们建议 T2DM 患者在预防或者治疗 CAVD 的过程中，早期可以加强对于患者血压、血糖及血脂的管理，通过监控患者的高血压、甘油三酯葡萄糖指数、总胆固醇/高密度脂蛋白比值、中性粒细胞/淋巴细胞比值和慢性肾脏病，特别是患者的高血压和甘油三酯葡萄糖指数，大大降低 CAVD 发生的风险。

参考文献

[1] Goody, P.R., Hosen, M.R., Christmann, D., Niepmann, S.T., Zietzer, A., Adam, M., *et al*. (2020) Aortic Valve Stenosis: From Basic Mechanisms to Novel Therapeutic Targets. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **40**, 885-900. https://doi.org/10.1161/atvbaha.119.313067

[2] Yadgir, S., Johnson, C.O., Aboyans, V., Adebayo, O.M., Adedoyin, R.A., Afarideh, M., *et al*. (2020) Global, Regional, and National Burden of Calcific Aortic Valve and Degenerative Mitral Valve Diseases, 1990-2017. *Circulation*, **141**, 1670-1680. https://doi.org/10.1161/circulationaha.119.043391

[3] DesJardin, J.T., Chikwe, J., Hahn, R.T., Hung, J.W. and Delling, F.N. (2022) Sex Differences and Similarities in Valvular Heart Disease. *Circulation Research*, **130**, 455-473. https://doi.org/10.1161/circresaha.121.319914

[4] Moncla, L.M., Briend, M., Bossé, Y. and Mathieu, P. (2023) Calcific Aortic Valve Disease: Mechanisms, Prevention and Treatment. *Nature Reviews Cardiology*, **20**, 546-559. https://doi.org/10.1038/s41569-023-00845-7

[5] Yu, G., Gong, X., Xu, Y., Sun, H., Liu, Y., Zhai, C., *et al*. (2023) The Global Burden and Trends of Four Major Types of Heart Disease, 1990-2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *Public Health*, **220**, 1-9. https://doi.org/10.1016/j.puhe.2023.04.005

[6] Otto, C.M. and Prendergast, B. (2014) Aortic-Valve Stenosis—From Patients at Risk to Severe Valve Obstruction. *New England Journal of Medicine*, **371**, 744-756. https://doi.org/10.1056/nejmra1313875

[7] Rajamannan, N.M., Evans, F.J., Aikawa, E., Grande-Allen, K.J., Demer, L.L., Heistad, D.D., *et al*. (2011) Calcific Aortic Valve Disease: Not Simply a Degenerative Process: A Review and Agenda for Research from the National Heart and

Lung and Blood Institute Aortic Stenosis Working Group: Executive Summary: Calcific Aortic Valve Disease—2011 Update. *Circulation*, **124**, 1783-1791. https://doi.org/10.1161/circulationaha.110.006767

[8] Abdul-Rahman, T., Lizano-Jubert, I., Garg, N., Talukder, S., Lopez, P.P., Awuah, W.A., *et al*. (2023) The Common Pathobiology between Coronary Artery Disease and Calcific Aortic Stenosis: Evidence and Clinical Implications. *Progress in Cardiovascular Diseases*, **79**, 89-99. https://doi.org/10.1016/j.pcad.2023.06.002

[9] Hsuan, C., Teng, S.I.F., Hsu, C., Liao, D., Chang, A.J., Lee, H., *et al*. (2023) Emerging Therapy for Diabetic Cardiomyopathy: From Molecular Mechanism to Clinical Practice. *Biomedicines*, **11**, Article 662. https://doi.org/10.3390/biomedicines11030662

[10] Chen, Y., Xiao, F. and Wang, R. (2022) Calcified Aortic Valve Disease Complicated with and without Diabetes Mellitus: The Underlying Pathogenesis. *Reviews in Cardiovascular Medicine*, **23**, Article 7. https://doi.org/10.31083/j.rcm2301007

[11] Kaur, R., Kaur, M. and Singh, J. (2018) Endothelial Dysfunction and Platelet Hyperactivity in Type 2 Diabetes Mellitus: Molecular Insights and Therapeutic Strategies. *Cardiovascular Diabetology*, **17**, Article No. 121. https://doi.org/10.1186/s12933-018-0763-3

[12] Kozakova, M., Morizzo, C., Goncalves, I., Natali, A., Nilsson, J. and Palombo, C. (2019) Cardiovascular Organ Damage in Type 2 Diabetes Mellitus: The Role of Lipids and Inflammation. *Cardiovascular Diabetology*, **18**, Article No. 61. https://doi.org/10.1186/s12933-019-0865-6

[13] Raddatz, M.A., Madhur, M.S. and Merryman, W.D. (2019) Adaptive Immune Cells in CALCIFIC aortic Valve Disease. *American Journal of Physiology-Heart and Circulatory Physiology*, **317**, H141-H155. https://doi.org/10.1152/ajpheart.00100.2019

[14] Driscoll, K., Cruz, A.D. and Butcher, J.T. (2021) Inflammatory and Biomechanical Drivers of Endothelial-Interstitial Interactions in Calcific Aortic Valve Disease. *Circulation Research*, **128**, 1344-1370. https://doi.org/10.1161/circresaha.121.318011

[15] Manduteanu, I., Simionescu, D., Simionescu, A. and Simionescu, M. (2021) Aortic Valve Disease in Diabetes: Molecular Mechanisms and Novel Therapies. *Journal of Cellular and Molecular Medicine*, **25**, 9483-9495. https://doi.org/10.1111/jcmm.16937

[16] Thaden, J.J., Nkomo, V.T. and Enriquez-Sarano, M. (2014) The Global Burden of Aortic Stenosis. *Progress in Cardiovascular Diseases*, **56**, 565-571. https://doi.org/10.1016/j.pcad.2014.02.006

[17] Corrigendum to: Training, Competence, and Quality Improvement in Echocardiography: The European Association of Cardiovascular Imaging Recommendations: Update 2020. *European Heart Journal-Cardiovascular Imaging*, **22**, 187. https://doi.org/10.1093/ehjci/jeaa347

[18] Otto, C.M., Nishimura, R.A., Bonow, R.O., Carabello, B.A., Erwin, J.P., Gentile, F., *et al*. (2020) 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, **143**, e35-e71. https://doi.org/10.1161/cir.0000000000000932

[19] Vahanian, A., Beyersdorf, F., Praz, F., Milojevic, M., Baldus, S., Bauersachs, J., *et al*. (2021) 2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal*, **43**, 561-632. https://doi.org/10.1093/eurheartj/ehab395

[20] Chambers, J.B., Garbi, M., Nieman, K., Myerson, S., Pierard, L.A., Habib, G., *et al*. (2017) Appropriateness Criteria for the Use of Cardiovascular Imaging in Heart Valve Disease in Adults: A European Association of Cardiovascular Imaging Report of Literature Review and Current Practice. *European Heart Journal-Cardiovascular Imaging*, **18**, 489-498. https://doi.org/10.1093/ehjci/jew309

[21] American Diabetes Association Professional Practice Committee (2021) 2. Classification and Diagnosis of Diabetes:*standards of Medical Care in Diabetes-2022*. *Diabetes Care*, **45**, S17-S38. https://doi.org/10.2337/dc22-s002

[22] Whelton, P.K., Carey, R.M., Aronow, W.S., Casey, D.E., Collins, K.J., Dennison Himmelfarb, C., *et al*. (2018) 2017 Acc/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*, **71**, 1269-1324. https://doi.org/10.1161/hyp.0000000000000066

[23] See, E.J. and Cullen, V. (2024) Commentary on the 2021 Update of the KDIGO Clinical Practice Guideline for Management of Blood Pressure in Chronic Kidney Disease. *Nephrology*, **30**, e14414. https://doi.org/10.1111/nep.14414

[24] Inker, L.A., Schmid, C.H., Tighiouart, H., Eckfeldt, J.H., Feldman, H.I., Greene, T., *et al*. (2012) Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *New England Journal of Medicine*, **367**, 20-29. https://doi.org/10.1056/nejmoa1114248

[25] Liu, X., Tan, Z., Huang, Y., Zhao, H., Liu, M., Yu, P., *et al*. (2022) Relationship between the Triglyceride-Glucose Index and Risk of Cardiovascular Diseases and Mortality in the General Population: A Systematic Review and Meta-Analysis. *Cardiovascular Diabetology*, **21**, Article No. 124. https://doi.org/10.1186/s12933-022-01546-0

[26] Sud, K., Narula, N., Aikawa, E., Arbustini, E., Pibarot, P., Merlini, G., *et al*. (2023) The Contribution of Amyloid Deposition in the Aortic Valve to Calcification and Aortic Stenosis. *Nature Reviews Cardiology*, **20**, 418-428. https://doi.org/10.1038/s41569-022-00818-2

[27] Shu, L., Yuan, Z., Li, F. and Cai, Z. (2023) Oxidative Stress and Valvular Endothelial Cells in Aortic Valve Calcification. *Biomedicine & Pharmacotherapy*, **163**, Article 114775. https://doi.org/10.1016/j.biopha.2023.114775

[28] Liu, X., Li, T., Sun, J. and Wang, Z. (2023) The Role of Endoplasmic Reticulum Stress in Calcific Aortic Valve Disease. *Canadian Journal of Cardiology*, **39**, 1571-1580. https://doi.org/10.1016/j.cjca.2023.07.025

[29] Yan, A.T., Koh, M., Chan, K.K., Guo, H., Alter, D.A., Austin, P.C., *et al*. (2017) Association between Cardiovascular Risk Factors and Aortic Stenosis: The CANHEART Aortic Stenosis Study. *Journal of the American College of Cardiology*, **69**, 1523-1532. https://doi.org/10.1016/j.jacc.2017.01.025

[30] Mosch, J., Gleissner, C.A., Body, S., *et al*. (2017) Histopathological Assessment of Calcification and Inflammation of Calcific Aortic Valves from Patients with and without Diabetes Mellitus. *Histol Histopathol*, **32**, 293-306.

[31] Yutzey, K.E., Demer, L.L., Body, S.C., Huggins, G.S., Towler, D.A., Giachelli, C.M., *et al*. (2014) Calcific Aortic Valve Disease: A Consensus Summary from the Alliance of Investigators on Calcific Aortic Valve Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **34**, 2387-2393. https://doi.org/10.1161/atvbaha.114.302523

[32] Davicevic, Z., Tavciovski, D. and Matunovic, R. (2010) Medical Treatments in Aortic Stenosis: Role of Statins and Angiotensin-Converting Enzyme Inhibitors. *Medicinski pregled*, **63**, 82-85. https://doi.org/10.2298/mpns1002082d

[33] O'Brien, K.D., Probstfield, J.L., Caulfield, M.T., Nasir, K., Takasu, J., Shavelle, D.M., *et al*. (2005) Angiotensin-Converting Enzyme Inhibitors and Change in Aortic Valve Calcium. *Archives of Internal Medicine*, **165**, 858-862. https://doi.org/10.1001/archinte.165.8.858

[34] Jia, G. and Sowers, J.R. (2021) Hypertension in Diabetes: An Update of Basic Mechanisms and Clinical Disease. *Hypertension*, **78**, 1197-1205. https://doi.org/10.1161/hypertensionaha.121.17981

[35] Cote, A.T., Phillips, A.A., Harris, K.C., Sandor, G.G.S., Panagiotopoulos, C. and Devlin, A.M. (2015) Obesity and Arterial Stiffness in Children: Systematic Review and Meta-Analysis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **35**, 1038-1044. https://doi.org/10.1161/atvbaha.114.305062

[36] Guerrero-Romero, F., Simental-Mendía, L.E., González-Ortiz, M., Martínez-Abundis, E., Ramos-Zavala, M.G., Hernández-González, S.O., *et al*. (2010) The Product of Triglycerides and Glucose, a Simple Measure of Insulin Sensitivity. Comparison with the Euglycemic-Hyperinsulinemic Clamp. *The Journal of Clinical Endocrinology & Metabolism*, **95**, 3347-3351. https://doi.org/10.1210/jc.2010-0288

[37] Liang, S., Wang, C., Zhang, J., Liu, Z., Bai, Y., Chen, Z., *et al*. (2023) Triglyceride-Glucose Index and Coronary Artery Disease: A Systematic Review and Meta-Analysis of Risk, Severity, and Prognosis. *Cardiovascular Diabetology*, **22**, Article No 170. https://doi.org/10.1186/s12933-023-01906-4

[38] Vasques, A.C.J., Novaes, F.S., de Oliveira, M.d.S., Matos Souza, J.R., Yamanaka, A., Pareja, J.C., *et al*. (2011) Tyg Index Performs Better than HOMA in a Brazilian Population: A Hyperglycemic Clamp Validated Study. *Diabetes Research and Clinical Practice*, **93**, e98-e100. https://doi.org/10.1016/j.diabres.2011.05.030

[39] Tao, L., Xu, J., Wang, T., Hua, F. and Li, J. (2022) Triglyceride-Glucose Index as a Marker in Cardiovascular Diseases: Landscape and Limitations. *Cardiovascular Diabetology*, **21**, Article No 68. https://doi.org/10.1186/s12933-022-01511-x

[40] Selig, J.I., Ouwens, D.M., Raschke, S., Thoresen, G.H., Fischer, J.W., Lichtenberg, A., *et al*. (2019) Impact of Hyperinsulinemia and Hyperglycemia on Valvular Interstitial Cells—A Link between Aortic Heart Valve Degeneration and Type 2 Diabetes. *Biochimica et Biophysica Acta* (*BBA*)-*Molecular Basis of Disease*, **1865**, 2526-2537. https://doi.org/10.1016/j.bbadis.2019.05.019

[41] Scatena, M., Jackson, M.F., Speer, M.Y., Leaf, E.M., Wallingford, M.C. and Giachelli, C.M. (2018) Increased Calcific Aortic Valve Disease in Response to a Diabetogenic, Procalcific Diet in the Ldlr$^{-/-}$ Apob$^{100/100}$ Mouse Model. *Cardiovascular Pathology*, **34**, 28-37. https://doi.org/10.1016/j.carpath.2018.02.002

[42] Zhang, L., Chen, S., Deng, A., Liu, X., Liang, Y., Shao, X., *et al*. (2015) Association between Lipid Ratios and Insulin Resistance in a Chinese Population. *PLOS ONE*, **10**, e0116110. https://doi.org/10.1371/journal.pone.0116110

[43] Chen, M., Meng, X., Han, Y., Yan, J., Xiao, C. and Qian, L. (2022) Profile of Crosstalk between Glucose and Lipid Metabolic Disturbance and Diabetic Cardiomyopathy: Inflammation and Oxidative Stress. *Frontiers in Endocrinology*, **13**, Article 983713. https://doi.org/10.3389/fendo.2022.983713

[44] Criqui, M.H. and Golomb, B.A. (1998) Epidemiologic Aspects of Lipid Abnormalities. *The American Journal of Medicine*, **105**, 48S-57S. https://doi.org/10.1016/s0002-9343(98)00212-5

[45] Imtiaz, F., Shafique, K., Mirza, S., Ayoob, Z., Vart, P. and Rao, S. (2012) Neutrophil Lymphocyte Ratio as a Measure of Systemic Inflammation in Prevalent Chronic Diseases in Asian Population. *International Archives of Medicine*, **5**, Article No. 2. https://doi.org/10.1186/1755-7682-5-2

[46] Zahorec, R. (2021) Neutrophil-to-Lymphocyte Ratio, Past, Present and Future Perspectives. *Bratislava Medical Journal*, **122**, 474-488. https://doi.org/10.4149/bll_2021_078

[47] Liu, Z., Liu, J., Wang, W., An, X., Luo, L., Yu, D., *et al*. (2023) Epigenetic Modification in Diabetic Kidney Disease. *Frontiers in Endocrinology*, **14**, Article 1133970. https://doi.org/10.3389/fendo.2023.1133970

[48] Einwoegerer, C.F. and Domingueti, C.P. (2018) Association between Increased Levels of Cystatin C and the Development of Cardiovascular Events or Mortality: A Systematic Review and Meta-analysis. *Arquivos Brasileiros de Cardiologia*, **111**, 796-807. https://doi.org/10.5935/abc.20180171

[49] Almén, M.S., Björk, J., Nyman, U., Lindström, V., Jonsson, M., Abrahamson, M., *et al*. (2019) Shrunken Pore Syndrome Is Associated with Increased Levels of Atherosclerosis-Promoting Proteins. *Kidney International Reports*, **4**, 67-79. https://doi.org/10.1016/j.ekir.2018.09.002

[50] Xhakollari, L., Jujic, A., Molvin, J., Nilsson, P., Holm, H., Bachus, E., *et al*. (2021) Proteins Linked to Atherosclerosis and Cell Proliferation Are Associated with the Shrunken Pore Syndrome in Heart Failure Patients. *PROTEOMICS—Clinical Applications*, **15**, e2000089. https://doi.org/10.1002/prca.202000089

[51] Hutcheson, J.D. and Goettsch, C. (2023) Cardiovascular Calcification Heterogeneity in Chronic Kidney Disease. *Circulation Research*, **132**, 993-1012. https://doi.org/10.1161/circresaha.123.321760

[52] Ternacle, J., Côté, N., Krapf, L., Nguyen, A., Clavel, M. and Pibarot, P. (2019) Chronic Kidney Disease and the Pathophysiology of Valvular Heart Disease. *Canadian Journal of Cardiology*, **35**, 1195-1207. https://doi.org/10.1016/j.cjca.2019.05.028

[53] The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (2014) Cardiovascular Disease, Chronic Kidney Disease, and Diabetes Mortality Burden of Cardiometabolic Risk Factors from 1980 to 2010: A Comparative Risk Assessment. *The Lancet Diabetes & Endocrinology*, **2**, 634-647. https://doi.org/10.1016/S2213-8587(14)70102-0

[54] Park, C.S., Han, K. and Kim, H. (2022) Response to Comment on Park *Et Al*. U-Shaped Associations between Body Weight Changes and Major Cardiovascular Events in Type 2 Diabetes Mellitus: A Longitudinal Follow-Up Study of a Nationwide Cohort of over 1.5 Million. Diabetes Care 2022; 45: 1239-1246. *Diabetes Care*, **45**, e188-e189. https://doi.org/10.2337/dci22-0038