Original Article

Predictors for coronary artery calcium score and differences in its distributions between populations with and without diabetes

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Abstract

Background and aims

Coronary artery calcium (CAC) scoring is a method of measure coronary plaque burden and has been shown as an excellent predictor for atherosclerotic cardiovascular disease (ASCVD). Diabetes mellitus (DM) is an established risk factor for ASCVD, but a certain portion of patients with DM do not have CAC (score = 0). We conducted a study to identify predictors of the CAC score other than DM and to compare distributions of the score between populations with and without DM.

Methods

We included participants who were referred to receive CAC scanning at a large imaging center from July 1992 to July 2020. The distribution of the CAC scores and baseline characteristics were compared between participants with and without DM. Univariate logistic regressions followed by multivariate analysis were performed using CAC score > 0 as outcome to identify independent factors contributing to the score.

Results

A total of 35,086 participants (mean age 58.9 ± 11.9 years, 63% male, 69% white) were included in the analysis. Of them, 11.8% had DM, 56% had hyperlipidemia, 38% had hypertension, and 7% were current smokers. A higher proportion of participants in the DM group had CAC score > 0 (82% vs 62%, p <0.01), but a substantial portion (18%) of DM patients had no CAC. Distribution of CAC score was also variable among participants with and without DM. Multivariate analysis showed that DM, age, male, hyperlipidemia, hypertension, and smoking were all independent predictors of CAC, and DM was associated with the second highest odds ratio (2.05, 95% confidence interval 1.87-2.25) behind male (4.55, 95% confidence interval 4.17-4.76).

Conclusions

While DM was the second strongest predictor of CAC, nearly one fifth of persons with DM had no detectable CAC. Among DM patients, there is significant heterogeneity of scores, so an individualized approach to primary prevention for these patients is warranted.

Keywords

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Introduction

Coronary artery calcium (CAC) scoring is a method of measuring coronary plaque burden using computed tomography (CT), and has emerged as an excellent predictor for future atherosclerotic cardiovascular disease (ASCVD) risk.[1] Specifically, CAC score has been found to associate with ASCVD events[2] and coronary heart disease (CHD)[2, 3] risk in 10 year follow up. Inclusion of CAC score in clinical decision making has been previously studied and compared to other risk factors.[4, 5] Diabetes mellitus (DM) is among the established risk factor for ASCVD,[6-8] and risk stratification for primary prevention of ASCVD depend highly on the presence or absence of DM.[6, 9] However, some studies suggest that the effect of DM on the development of ASCVD might be heterogeneous.[10, 11] Furthermore, a certain portion of patients with DM who do not have evidence of subclinical atherosclerosis (CAC=0) was found to be as high as 37%.[11]

With the suggested heterogeneity of DM, there are likely variabilities among CAC scores in patients with and without DM. The way DM can vary distributions among patients in different age groups and sex has not been previously studied. To identify predictors of the CAC score other than DM and to compare distributions of the score between populations with and without DM, we conducted an observational study using a large cohort.

Methods

Patient Selection

We included participants from patients without known cardiovascular disease who were referred to a medical center for a CAC scan from July 1992 to July 2020. For participants with multiple visits, only the first visits were included. Baseline characteristic and risk factor data were collected using self-reported surveys, including age, sex, race, DM, hyperlipidemia, hypertension, and smoking. Candidates who were less than

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20 years old or had missing data for DM or other risk factors were excluded.

CAC scoring

CAC data was collected using non-contrast, cardiac gated CT scans. CAC scores were obtained using the Agatston method.[12] The scores were further divided into groups of no CAC (CAC=0), mild CAC (CAC= 1-99), moderate CAC (CAC=100-399), and severe CAC (CAC>400).

Statistical Analysis

All continuous variables are reported in mean and standard deviation, and binary and categorical variables are reported in count and percentage. Differences in baseline characteristics between participants with and without DM were evaluated using chi square tests. For comparison, age was further stratified into quartiles (< 51 years, 51-59 years, 59-67 years, > 67 years). We used logistic regression to identify predictors for CAC using CAC score > 0 as the outcome. Univariate analyses were first performed to evaluate the individual known risk factors for ASCVD. A multivariate model which included all potential predictors studied was used to further identify independent predictors. All analyses were performed using SAS for Windows, and all statistical tests were performed at a two tailed significance level of 0.05.

Results

A total of 74,644 data points were collected for this study. After removing multiple visits by the same subjects and missing DM data, 35,086 participants were included in the analysis. Participants were further divided in groups with (12%) and without (88%) DM. The mean age of the cohort was 58.9 (11.9) years, 22,036 (63%) were male, and 24,060 (69%) were white. In patients with DM, prevalence of risk factors like hyperlipidemia, hypertension, and smoking were all higher. Percentage of participants with CAC score > 0 was higher in the DM group (82% vs 62%, p <0.01), but a substantial proportion of them (18%) had no detectable CAC (score = 0) (Figure 1).

When participants were divided into 8 subgroups by sex and age in quartiles, diabetic males had the highest percentage of CAC score > 0, followed by non-diabetic males, diabetic females, and non-diabetic females across all age groups (Figure 2). In further analysis of 4 subgroups by sex and DM, percentage of CAC score > 0 decreased with age and percentage of CAC score > 400 increased with age. In females, percentage of CAC score between 1 and 99 increased with age in participants without DM but was similar (between 30% and 34%) across the age groups in participants with DM (Figure 2). The percentage of CAC score between 100 and 399 increased with age in both participants with and without DM. In males without DM, the percentage of CAC score between 1 and

Table 1. Baseline characteristics

	Total (n=35,086)	Diabetes (n=4,129)	No Diabetes (n=30,957)	*p*-value
Age (years)	58.9 ± 11.9	62.5 ± 11.2	58.6 ± 11.6	<0.01
Male	22,036 (63)	2,578 (62)	19,556 (63)	0.35
Race				
African-American	1,509 (4)	356 (9)	1,153 (4)	<0.01
American-Indian	58 (0)	6 (0)	52 (0)	
Asian	3,759 (11)	696 (17)	3,063 (10)	
Asian-Indian	517 (1)	128 (3)	389 (1)	
Hawaiian/Pacific	96 (0)	20 (0)	76 (0)	
Hispanic/Latino	3,818 (11)	947 (23)	2,871 (9)	
Other	1,269 (4)	186 (5)	1,083 (3)	
White	24,060 (69)	1,790 (43)	22,270 (72)	
Risk Factors				
Diabetes	4,146 (12)	4,146 (100)	-	
Hyperlipidemia	19,678 (56)	2,774 (67)	16,904 (55)	<0.01
Hypertension	13,225 (38)	2,750 (67)	10,475 (34)	<0.01
Current Smoker	2,355 (7)	349 (8)	2,006 (6)	<0.01
CAC				
CAC=0	12,456 (36)	752 (18)	11,704 (38)	<0.01
CAC>0	22,630 (64)	3,377 (82)	19,253 (62)	
CAC=1-99	10,975 (31)	1,125 (27)	9,850 (32)	<0.01
CAC=100-399	5,454 (16)	774 (19)	4,680 (15)	
CAC>400	6,201 (18)	1,478 (36)	4,723 (15)	

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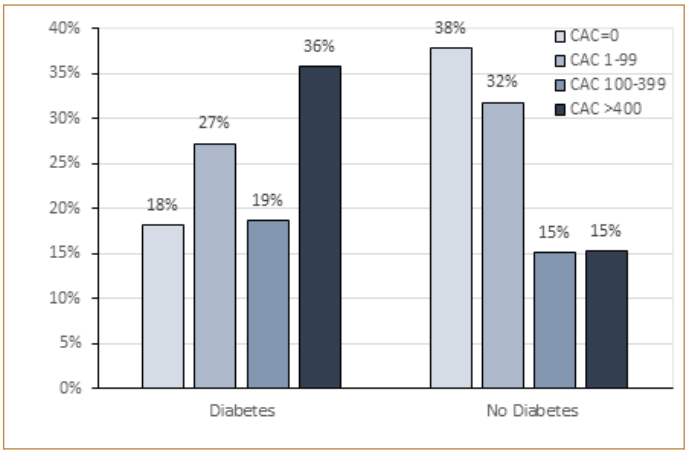


Figure 1. Distribution of CAC in patients with and without DM

99 first increased then decreased with age, with the highest percentage in the 51-59 age group. The percentage of the same CAC score category decreased constantly with age in the DM group. The changing pattern of the percentage of CAC between 100 and 399 across age groups was similar between male participants with and without DM.

In univariate analysis, DM, age, hyperlipidemia, hypertension, smoking, and male were all associated with increased odds ratios (ORs) of having detectable CAC. Race was also a significant predictor of CAC > 0. In multivariate analysis, DM, age, hyperlipidemia, hypertension, smoking, and male appeared to be independent predictors of CAC > 0. DM had the second highest OR in both the univariate analysis (2.73; 95% confidence interval [95% CI]: 2.51-2.96) and after adjusting for other variables in the multivariate analysis (2.11; 95% CI: 1.92-2.32) (Table 2). Male sex was the strongest risk factor for having CAC, with an adjusted OR of 4.46 (4.23-4.71).

Discussion

DM is a known risk factor for cardiovascular disease. Current guidelines recommend all patients age 40-75 years to be started on a statin regardless of ASCVD risk.[6,9] Implementation of CAC score is recommended in patients with intermediate risk of ASCVD without DM.[9] However, within our cohort we observed a variability of distribution of CAC scores among patients with DM. Particularly, we saw that 18% of patient with diabetes did not have coronary disease. Malik et al.[11] saw a larger portion of diabetic patients without CAC in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort when compared to ours. The differences in subclinical atherosclerosis can likely be explained by differences in patient population, as we had a primarily white population as compared to the multiethnic population in the MESA. Besides the differences in prevalence of CAC, we observed more patients with mild disease than moderate disease (27% vs. 19%), and percentage of patients with severe disease was the highest within the DM group. This is in contrast with participants without DM, in whom we saw the highest

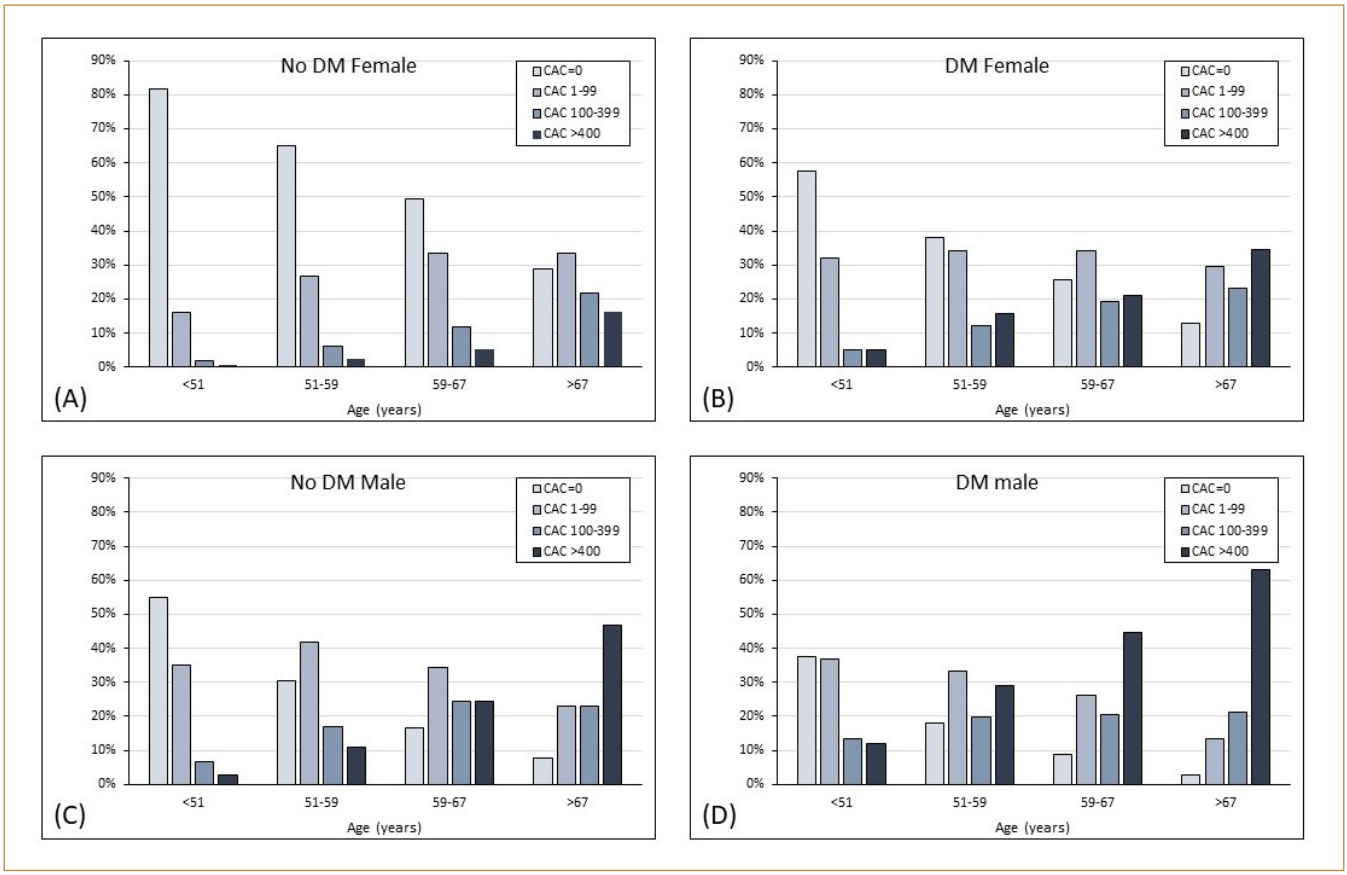


Figure 2. CAC distribution by age and sex subgroups

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Table 2. Multivariate Analysis of Cardiac Risk Factors and CAC>0

Variable	Odds Ratio (Univariate)	Odds Ratio (Multivariate)
Diabetes	2.73 (2.51-2.96)[b]	2.11 (1.92-2.32)[b]
Age	1.08 (1.08-1.09)[b]	1.09 (1.09-1.10)[b]
Hyperlipidemia	1.94 (1.85-2.03)[b]	1.62 (1.54-1.71)[b]
Hypertension	2.50 (2.39-2.63)[b]	1.72 (1.63-1.82)[b]
Smoking	1.14 (1.05-1.25)[a]	1.31 (1.18-1.45)[b]
Race	0.95 (0.93-0.96)[b]	0.96 (0.94-0.98)[b]
Male	2.76 (2.64-2.89)[b]	4.46 (4.23-4.71)[b]

[a]p <0.05, bp <0.01

percentage was constituted by those without disease, with similar prevalence of moderate and severe disease. Previous studies had described the utility of adding CAC as part of risk classification in patients with metabolic syndrome and DM,[10,11] and patients with CAC=0 who had DM over 10 years showed similar low risk as patients with DM of less than 10 years.[11] Our study confirms that DM alone may not be sufficient for accurate risk stratification for ASCVD, as shown by the highly variable distribution of CAC score among patients.

When the population was stratified by age and sex, we found that DM also modified distribution of CAC. Across all subgroups, percentage of patients without CAC decreases with age and percentage of patients with severe disease increases in age. However, we observed great variability of distribution within the mild and moderate disease. In females without DM, we saw a general trend of increased CAC as age increases, with similar prevalence of mild disease in the 59-67 and >67 age group. However, in females with DM, percentage of patients with mild disease were similar across all age groups. Conversely, males without DM did not show a general trend between mild disease and age, while males with DM showed a decrease in mild disease as age increases. The association between CAC and cardiovascular outcomes has been studied in different age groups.[13-17] Among younger adults, CAC is associated with increased risk of cardiovascular disease and death.[14,16] In older populations, CAC appears to be a better predictor for cardiovascular disease when compared to age.[13] Our cohort fell largely in an intermediate age group with a mean of 58.9 years. Although we saw a general trend of increasing prevalence of CAC>0 with increase in age, the presence of CAC seems to vary greatly depending on age, sex, and presence of DM. We have shown similar distribution of atherosclerosis using cardiac CT angiography in young persons with diabetes, confirming our observations with CAC in this study.[18]

Differences in CAC score among men and women and its correlating mortality have also been previously described.[19-21] Within our cohort we found that females with DM had lower prevalence of CAC>0 than males without DM across all age groups. This is consistent with the multivariate analysis, in which we saw that male was associated with nearly 5-fold risk for CAC > 0 while DM was only 2-fold. Female sex is known to be protective against ASCVD, and protective effects seems to be multifactorial. Factors such as sex hormones and differences in calcified plaque in between males and females has been described in literature.[22, 23] Although DM plays a role in the development of ASCVD, observations from our cohort suggest that it might not be as critical as compared to other factors described above. The role of DM in relation to other factors that might contribute to differences in CAC between the two sexes should be further studied.

There are several limitations in this study. Although the association between CAC and cardiovascular end points has been established, this study is observational and did not include any cardiovascular end points. Our study did not account for the severity of DM using quantitative data such as hemoglobin A1C, which might have contributed to the variability of CAC distribution. Risk factors were collected based on patient survey instead of objective laboratory data. The DM group had significantly higher percentage of cardiovascular risk factors such as hyperlipidemia, hypertension, and smoking. However, we controlled for these variables when performing multivariate analysis.

In conclusion, DM is a disease with great heterogeneity, altering the severity of CAC among different sex and age groups. An individualized approach should be used when risk stratifying patients for primary prevention of ASCVD.

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References

1. Greenland P, Blaha MJ, Budoff MJ, et al. Coronary Calcium Score and Cardiovascular Risk. Journal of the American College of Cardiology. 2018-07-01 2018;72(4):434-447. doi:10.1016/j.jacc.2018.05.027
2. Budoff MJ, Young R, Burke G, et al. Ten-year Association of Coronary Artery Calcium with Atherosclerotic Cardiovascular Disease (ASCVD) Events: the Multi-ethnic Study of Atherosclerosis (MESA). Eur Heart J. Jul 1 2018;39(25):2401-2408. doi:10.1093/eurheartj/ehy217
3. McClelland RL, Jorgensen NW, Budoff M, et al. 10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors: Derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) With Validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). J Am Coll Cardiol. Oct 13 2015;66(15):1643-53. doi:10.1016/j.jacc.2015.08.035
4. Grandhi GR, Mirbolouk M, Dardari ZA, et al. Interplay of Coronary Artery Calcium and Risk Factors for Predicting CVD/CHD Mortality: The CAC Consortium. JACC Cardiovasc Imaging. May 2020;13(5):1175-1186. doi:10.1016/j.jcmg.2019.08.024
5. Blaha MJ, Cainzos-Achirica M, Greenland P, et al. Role of Coronary Artery Calcium Score of Zero and Other Negative Risk Markers for Cardiovascular Disease. Circulation. 2016-03-01 2016;133(9):849-858. doi:10.1161/circulationaha.115.018524
6. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2019. Diabetes Care. 2019-01-01 2019;42(Supplement 1):S103-S123. doi:10.2337/dc19-s010
7. Collaboration TERF. Diabetes Mellitus, Fasting Blood Glucose Concentration, and Risk of Vascular Disease: a Collaborative Meta-analysis of 102 Prospective Studies. The Lancet. 2010-06-01 2010;375(9733):2215-2222. doi:10.1016/s0140-6736(10)60484-9
8. Menon V, Kumar A, Patel DR, et al. Impact of Baseline Glycemic Control on Residual Cardiovascular Risk in Patients With Diabetes Mellitus and High-Risk Vascular Disease Treated With Statin Therapy. Journal of the American Heart Association. 2020-01-07 2020;9(1)doi:10.1161/jaha.119.014328
9. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019-06-18 2019;139(25)doi:10.1161/cir.0000000000000625
10. Agarwal S, Cox AJ, Herrington DM, et al. Coronary Calcium Score Predicts Cardiovascular Mortality in Diabetes: Diabetes Heart Study. Diabetes Care. 2013-04-01 2013;36(4):972-977. doi:10.2337/dc12-1548
11. Malik S, Zhao Y, Budoff M, et al. Coronary Artery Calcium Score for Long-term Risk Classification in Individuals With Type 2 Diabetes and Metabolic Syndrome From the Multi-Ethnic Study of Atherosclerosis. JAMA Cardiology. 2017-12-01 2017;2(12):1332. doi:10.1001/jamacardio.2017.4191
12. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of Coronary Artery Calcium using Ultrafast Computed Tomography. Journal of the American College of Cardiology. 1990-03-01 1990;15(4):827-832. doi:10.1016/0735-1097(90)90282-t
13. Yano Y, O'Donnell CJ, Kuller L, et al. Association of Coronary Artery Calcium Score vs Age With Cardiovascular Risk in Older Adults. JAMA Cardiology. 2017-09-01 2017;2(9):986. doi:10.1001/jamacardio.2017.2498
14. Carr JJ, Jacobs DR, Terry JG, et al. Association of Coronary Artery Calcium in Adults Aged 32 to 46 Years With Incident Coronary Heart Disease and Death. JAMA Cardiology. 2017-04-01 2017;2(4):391. doi:10.1001/jamacardio.2016.5493
15. Okwuosa TM, Greenland P, Ning H, et al. Yield of Screening for Coronary Artery Calcium in Early Middle-Age Adults Based on the 10-Year Framingham Risk Score. JACC: Cardiovascular Imaging. 2012-09-01 2012;5(9):923-930. doi:10.1016/j.jcmg.2012.01.022
16. Miedema MD, Dardari ZA, Nasir K, et al. Association of Coronary Artery Calcium With Long-term, Cause-Specific Mortality Among Young Adults. JAMA Network Open. 2019-07-19 2019;2(7):e197440. doi:10.1001/jamanetworkopen.2019.7440
17. Nakanishi R, Li D, Blaha MJ, et al. All-cause Mortality by Age and Gender Based on Coronary Artery Calcium Scores. European Heart Journal – Cardiovascular Imaging. 2016-11-01 2016;17(11):1305-1314. doi:10.1093/ehjci/jev328
18. Nezarat N, Budoff MJ, Luo Y, et al. Presence, Characteristics, and Volumes of Coronary Plaque Determined by Computed Tomography Angiography in Young Type 2 Diabetes Mellitus. Am J Cardiol. May 15 2017;119(10):1566-1571. doi:10.1016/j.amjcard.2017.02.023
19. Kelkar AA, Schultz WM, Khosa F, et al. Long-Term Prognosis After Coronary Artery Calcium Scoring Among Low-Intermediate Risk Women and Men. Circulation: Cardiovascular Imaging. 2016-04-01 2016;9(4):e003742. doi:10.1161/circimaging.115.003742
20. Shaw LJ, Bugiardini R, Merz CNB. Women and Ischemic Heart Disease. Journal of the American College of Cardiology. 2009-10-01 2009;54(17):1561-1575. doi:10.1016/j.jacc.2009.04.098
21. Kavousi M, Desai CS, Ayers C, et al. Prevalence and Prognostic Implications of Coronary Artery Calcification in Low-Risk Women. JAMA. 2016-11-22 2016;316(20):2126. doi:10.1001/jama.2016.17020
22. Subramanya V, Zhao D, Ouyang P, et al. Association of Endogenous Sex Hormone Levels with Coronary Artery Calcium Progression Among Post-menopausal Women in the Multi-Ethnic Study of Atherosclerosis (MESA). Journal of Cardiovascular Computed Tomography. 2019-01-01 2019;13(1):41-47. doi:10.1016/j.jcct.2018.09.010
23. Shaw LJ, Min JK, Nasir K, et al. Sex Differences in Calcified Plaque and Long-term Cardiovascular Mortality: Observations from the CAC Consortium. European Heart Journal. 2018-11-01 2018;39(41):3727-3735. doi:10.1093/eurheartj/ehy534

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