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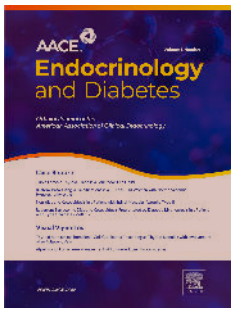

Cardiometabolic disease–associated markers begin to increase at an A1C >5%

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PII: S3050-9157(26)00167-0

DOI: https://doi.org/10.1016/j.aed.2026.07.019

Reference: AED 648

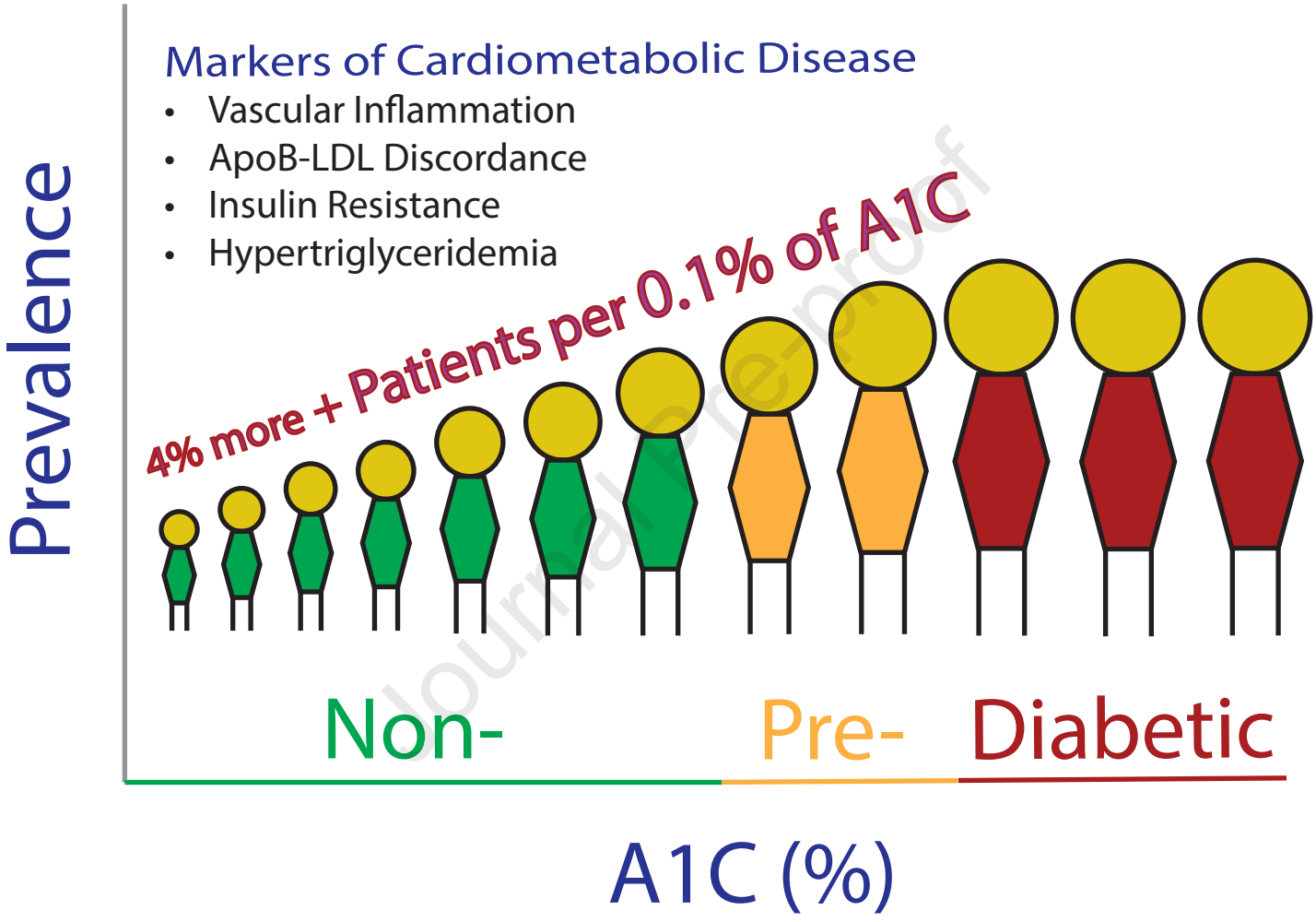
To appear in: *AACE Endocrinology and Diabetes*

Received Date: 30 June 2026

Revised Date: 22 July 2026

Accepted Date: 24 July 2026

Please cite this article as: Penn MS, Winchester TB, Saghir J, Koney A, Latsko MS, Dixit SB, Eckel RH, Saghir M, Cardiometabolic disease–associated markers begin to increase at an A1C >5%, *AACE Endocrinology and Diabetes* (2026), doi: https://doi.org/10.1016/j.aed.2026.07.019.



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Keywords:
Diabetes
Vascular inflammation
Hyperlipidemia
Metabolic syndrome

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Acknowledgements: None

Funding: There was no funding for this study.

Conflicts of Interest:
Marc S. Penn, MD, PhD, FACC – Paid consultant for Quest Diagnostics, Inc. with no equity interest.

Trisha B. Winchester, PhD, Ayorkor Koney, Maeson S. Latsko, PhD, Sanjay B. Dixit, DO and Mouris Saghir, PhD, are employees of Quest Diagnostics, Inc, and as such receive salary and in some cases equity in the company.

Robert H. Eckel, MD and John Saghir – No conflicts of interest to disclose

Contributions
MS, MSP, TBW – Conceived of study
AK, MSP, TBW, MSL – Obtained, reviewed and finalized data
JS, MS, MSP, RHE, SBD – Data analyses and interpretation
JS, MSL, MSP, RHE – Manuscript preparation
MSP – Wrote the first draft of the manuscript
All Authors – Manuscript review and finalization

MSP is the guarantor of this work and, as such, had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis

The datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Patient Consent was not required. As a secondary analysis of existing data that were deidentified, this study does not constitute human subjects research as defined at 45 CFR 46.102 and thus did not require IRB review

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JS, MSL, MSP, RHE – Manuscript preparation
MSP – Wrote the first draft of the manuscript
All Authors – Manuscript review and finalization

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Abstract

Introduction: Risk of atherosclerosis and cardiovascular events increases as a function of increasing hemoglobin A1C (A1C), even in patients with normal A1C (<5.7%). Our objective was to determine whether increasing A1C correlates to increasing atherogenic particles (measured as apoB LDL-C discordance), vascular inflammation, and/or worsening metabolic disease.

Method: We queried the national laboratory information system of the Quest Center for Excellence for Cardiometabolic Testing at Cleveland HeartLab for all persons who had an A1C and apoB simultaneously measured in 2021-22.

Results: We identified 127,141 outpatients who had both tests simultaneously performed during the study period: average age of 61.6±14.4 years, 52% female, and 63.4% with an A1C <5.7%. LDL-C and apoB levels did not correlate with A1C, peaking at an A1C of 5.2% (108.9±36.4 mg/dL [LDL-C] and 91.5±25.2 mg/dL [apoB]). In contrast, the increased prevalence of apoB-LDL-C discordance correlated strongly with increasing A1C (r^2=0.95), as did prevalence of vascular inflammation (r^2=0.97), hypertriglyceridemia (r^2=0.96), and insulin resistance (r^2=0.95). Using these 4 markers, each 0.1% increase in A1C (between 5% and 5.7%) correlated with a 4% increase in the number of patients with early evidence of cardiometabolic disease.

Discussion: We identified a high-risk population, approaching 50% of people with 5%≤A1C<5.7%, who otherwise may be told their biomarker levels are within a “normal” range. Identifying these individuals at an early stage of cardiometabolic dysfunction could motivate aggressive lifestyle or pharmacological measures that reverse their condition and prevent disease.

Introduction

Since the Scandinavian Simvastatin Survival Study trial in the 1990's, approaches to lowering cholesterol and low-density lipoprotein (LDL) cholesterol (LDL-C)[1] have successfully reduced LDL levels[2] with a resultant decrease in myocardial infarction and cardiovascular death [3, 4]. However, despite maintaining the decrease in cholesterol and LDL-C, since 2010, the prevalence of myocardial infarction and cardiovascular death has been on the rise [5]. Recent updates to the AHA/ACC guidelines for cardiovascular prevention have put forth a call to action to promote further lowering of LDL cholesterol in individuals with coronary artery disease, as well as to more aggressively test and treat people at an early age [6]. This focus on LDL cholesterol is without evidence that increases in cardiovascular death are correlated with LDL cholesterol levels in the population [6]. There is growing recognition that the increase in cardiovascular disease, chronic kidney disease and metabolic-dysfunction associated steatotic liver disease are due to an increase in the prevalence of cardiometabolic disease [5, 7, 8]. This recognition led to the recent release of the first CKM guidelines [9]. While these guidelines are a significant advance in our recognition of the consequences of cardiometabolic disease, there remains a real opportunity to define how to recognize persons who are elevated risk of cardiometabolic disease and its consequences long before they reach what the guidelines call Stage 1 CKM syndrome [10].

Diabetes is defined as a hemoglobin A1C (A1C) of $\geq$6.5%, in part because these A1C values were noted to increase risk for patients in the Diabetes Control And Complications Trials developing microvascular complications [11]. There is growing evidence that hyperglycemia <6.5% is associated with an increase in cardiovascular disease [12-15]. A1C values included in the definition of prediabetes (5.7%$\leq$ A1C<6.5%) have helped identify patients at increased cardiovascular risk *prior* to being diagnosed with diabetes [16]. While a meaningful advance, more recent studies have suggested that increasing A1C in the "normal" range can be associated with increased cardiometabolic disease and atherosclerotic burden [10, 17]. Thus, people early in their journey of developing cardiometabolic disease are at risk of receiving a false sense of security of having limited risk if testing is limited to A1C and LDL-cholesterol. Identifying individuals early in the development of cardiometabolic disease is important because earlier changes in towards a heart-healthy lifestyle are more likely to prevent developing cardiovascular disease [18, 19].

The goal of this study was to investigate a real-world population data using biomarker data from a laboratory information system to determine if there is a correlation between A1C and the presence of biomarkers of cardiometabolic disease. We studied deidentified data from the the national laboratory information system of the Quest Center for Excellence for Cardiometabolic Testing at Cleveland HeartLab for the 127,141 of individuals who had simultaneous A1C and apoprotein B (apoB) testing in 2021-22. Specifically, we analyzed biomarkers of dyslipidemia, insulin resistance, and vascular inflammation as a function of A1C to determine at what level of A1C cardiometabolic disease began to develop. Our findings demonstrate a correlation between increased cardiometabolic disease and A1C beginning with an A1C of 5%.

Methods

This retrospective study examined associations between blood-based biomarkers and A1C. Test results from deidentified patients were captured from the national laboratory information system of the Quest Center for Excellence for Cardiometabolic Testing at Cleveland HeartLab of all patients who had an A1C and apoB measured with the same blood draw in 2021 and 2022. This was a limited dataset (as defined by https://www.hhs.gov/hipaa/for-professionals/special-topics/research/index.html) which only captured patient sex, age and results for simultaneously measured A1C, apoB, and additional cardiometabolic biomarkers. No current or past medical history, nor medication profiles were available. The number of individuals with specific subsets of measures are detailed in Results. As a secondary analysis of existing data that were deidentified, this study does not constitute human subjects research as defined at 45 CFR 46.102 and thus does not require IRB review.

Extracted data were filtered by transforming all test results that indicated a value above or below the test analytical range (using a "<" or ">") to their numeric value. Clinical cutoffs for A1C used in the study were based on persons without diabetes (<5.7%), with prediabetes (5.7% to 6.4%), and with diabetes (≥6.5%). The following cardiometabolic and inflammatory biomarker value were used to define an elevated value: myeloperoxidase (MPO) ≥470 pmol/L (moderate CVD risk or greater),[20]; high sensitivity C-reactive protein (hsCRP) >2.0 mg/L (average CVD risk or greater); insulin resistance score (IRS) >66% (high IR risk),[21]; triglycerides (TG) >150 mg/dL; LDL-C ≥100 mg/dL; and apoB ≥90 mg/dL (moderate CVD risk or greater). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Statistical Analysis

Patient baseline characteristics were summarized using standard statistics, including mean (standard deviation, SD) for normally distributed continuous variables and n (%) for categorical variables. Correlations are based on fits of the data to a line with the r^2 reported. Analyses were performed with Microsoft EXCEL v16.95 (Redmond, WA, USA). As stated above, the only clinical data available were age and gender; therefore, no analyses could be done to adjust for possible confounders including blood pressure, body mass index or concurrent medications.

Results

Figure 1 depicts the distribution in A1C values of the total cohort: 127,141 persons who had simultaneous A1C and apoB blood testing in 2021 and 2022 ordered through a large national laboratory with the results in the information system of the Quest Center for Excellence for Cardiometabolic Testing at Cleveland HeartLab. The mean age of the population was 61.6±14.4 years and 52% of the population was female.

Of the total cohort, 63.4% (80,607) did not have prediabetes or diabetes (A1C <5.7%) and 18.6% (15,027) of those without prediabetes or diabetes had simultaneous blood testing that included an MPO, IRS, and a lipid panel. Of that group, 28.4% (4,269) of patients had an A1C <5%, and 71.6% (10,758) of patients made up the final analysis subcohort (5.0%≤A1C≤5.7%, mean age 58.0±14.5 years, 58% female).

The distribution of low density lipoprotein (LDL-C), apoB and high density lipoprotein cholesterol (HDL-C), non-HDL-C values for all patients with an 4.5%≤A1C≤ 7% as a function of A1C are shown in Figure 2A. LDL-C, apoB, and non-HDL-C levels did not correlate with A1C, peaking at an A1C of 5.2% (108.9±36.4 mg/dL [LDL-C], 91.5±25.2 mg/dL [apoB], and 129.3±34.2 mg/dL [non-HDL-C]). Figure 2B demonstrates that based on moderate to high-risk cutoffs an LDL-C >100 mg/dL, an apoB of >90 mg/dL[22] and a non-HDL-C of >130 mg/dL, upwards of 40% to 60% of patients with an A1C between 5% and 6% continue to have elevated lipid parameters depending on which parameter is being assessed. Figure 2C demonstrates that despite declining lipid parameters with an A1C above 5.2%, apoB-LDL-C discordance based on moderate to high-risk cutoffs increases linearly (r^2=0.95 through A1C of 6.4%) as a function of A1C beginning with an A1C of 5%.

Triglycerides (Figure 2D) and the percent of patients with a triglycerides above 150 mg/dL (Figure 2E) increase as a function of A1C (r^2=0.96, TG and r^2=0.96, % patients with high TG) beginning with an A1C of 5%. Triglycerides continue to increase with A1C despite the data showing the LDL-C, apoB and non-HDL-C decline above an A1C of 5.2% (Figure 2A). Beginning with an A1C of 5% there is a trend toward increasing percentage of patients with apoB-LDL-C discordance that have hypertriglyceridemia increases from 45% to 70%, weakly correlated as a function of A1C (r^2=0.35 through an A1C of 6.4%) (Figure 2F).

Because increasing presence of apoB-LDL-C discordance with increasing A1C, suggests increasing levels of more atherogenic small dense LDL particles,[23] we investigated whether there was a relationship to vascular inflammation as measured by MPO. Figure 3A shows an increase in MPO based on A1C starting at an A1C of 5% (r^2=0.97 through an A1C of 6.4%). Greater than 40% of the population had an hsCRP>2.0, and no correlation was observed between hsCRP >2.0 and A1C (r^2=0.17) (data not shown).

We also assessed to what extent the presence of insulin resistance increased as a function of A1C. As seen in Figure 3B, beginning at an A1C of 5%, the percent of patients who were at risk for having insulin resistance (>66% based on IRS),[21] increased almost 7 fold from 6% to 41% at an A1C of 6.4% (r^2=0.95).

Using 4 biomarkers of cardiometabolic disease that correlated with A1C, namely apoB-LDL-C discordance, hypertriglyceridemia, MPO and IRS, we investigated the utility of these markers in reclassifying patients for risk in the normal range of A1C between 5.0% and <5.7%. We further determined whether there was redundancy in the markers.

As seen in Figure 4A, the number of patients who exhibited abnormal markers of cardiometabolic disease increased from 21% to 50% between an A1C of 5% and 5.7% with the majority of patients only having a single marker positive (18% to 34%). With increasing A1C, the number of patients with 2 biomarkers positive increased from 2% to 13%. Very few patients had 3 biomarkers positive, and no patient had all 4 biomarkers elevated. Figure 4B shows the trend of each individual marker as a function of A1C between 5.0% and 5.7%. These data demonstrate that hypertriglyceridemia and measures of insulin resistance are the most common markers of cardiometabolic disease that are elevated. However, each of these are elevated as isolated markers in only 10% of the patients at an A1C of 5.7% (data not shown). The data in Figure 4C show that for every 0.1% increase in A1C between 5% and 5.7%, 4% more patients are identified to have at least 1 positive cardiometabolic risk marker (r^2=0.99).

Discussion

The growing prevalence of cardiometabolic disease, including obesity, metabolic syndrome, and type 2 diabetes in the Western world, has reversed a decades long trend of lowering rates of myocardial infarction [5, 7]. Due to the commonality of risk factors, the increases in cardiovascular disease are associated with increases in other diseases including chronic kidney disease and fatty liver disease [24-26]. Central to patients developing cardiometabolic risk are alterations leading to dysglycemia [27, 28], inflammation [29, 30], and specific metabolic impacts on the standard lipid profile [23]. For example, increases in small dense LDL particles have recently been shown to be associated with an increased prevalence of elevated coronary calcium scores [31]. Further supporting the importance of broader biomarkers assessment to assess risk, is a recent study with long-term follow-up of patients from the Diabetes Prevention Program and the Diabetes Prevention Program Outcomes Study with prediabetes showed that not all patients with dysglycemia are the same, and that deeper phenotyping is critical [32].

A1C is accepted as a tool for screening people for prediabetes (A1C of 5.7% to 6.4%) and type 2 diabetes (A1C $\geq$ 6.5%) [33]. While there is clearly increasing risk of macro- and micro- vascular disease at these A1C levels, recent studies have demonstrated increasing prevalence of atherosclerosis and clinical events in patients in the normal range of A1C <5.7% [10].

Thus, the current focus of the updated guidelines on LDL-C testing and lowering does not take advantage of the potential of individual phenotyping with relative simple tests across the cardiometabolic spectrum of disease to identify those who may benefit from LDL-C lowering [6]. Worse yet, the clinical focus on measuring A1C and LDL-C can result in large subset of a "normal" population being reassured of their blood measures, while underlying unrecognized cardiometabolic disease could festers for years. Diet and exercise are important components of the clinical treatment of obesity, type 2 diabetes, and coronary artery disease, especially during the early phase of these conditions when motivation of the patients can have the greatest impact. Unfortunately, patients are often being reassured "everything is okay" instead of receiving measurable and modifiable motivational insights into their true risks for a future diagnosis of chronic disease that could be modified through lifestyle of LDL-C lowering as supported by the recent guidelines for prevention [6].

Our study identified that cardiometabolic disease biomarkers in a real-world cohort increase as a function of A1C before people are diagnosed with prediabetes or diabetes. This is consistent with imaging studies that demonstrate the presence of atherosclerosis in a significant number of patients with A1C<5.7% [10]. Notably, physicians appear to start treatment to lower LDL-C on a population basis beginning with an A1C of 5.2% (Figure 1A); however, 40% to 60% of the population with an A1C between 5.0% and 5.7% remain undertreated or untreated based on a goal of <100 mg/dL (Figure 1B) and TG levels that continue to increase (Figure 2A and B). The addition of apoB as a biomarker identified up to an additional 10% of patients who may have sufficiently treated LDL-C but, because of metabolic remodeling of LDL particles, have apoB-LDL-C discordance indicating that they need more aggressive LDL-C lowering as well as additional assessment for insulin resistance and inflammation [23, 34, 35]. Interestingly, although non-

HDL-C was highly correlated with LDL-C it did not offer unique or even redundant insight of metabolic risk over TG and apoB. These data support more aggressive lipid lowering and moreover, suggest a strategy to identifying those patients who may benefit from more aggressive LDL-C lowering goals.

Defining the presence of cardiometabolic disease with IRS, MPO, TG, and apoB-LDL-C discordance there is a 4% increase of individuals with evidence of cardiometabolic disease per 0.1% increase in A1C over the range of 5% to 5.7% (Figure 4C). Each marker identifies offers distinct insight into developing cardiometabolic disease. ApoB shows that as A1C increases, the percentage of patients who have apoB-LDL-C discordance significantly increases. These patients have elevated LDL particle number that are considered pro-atherogenic [23, 31, 34, 35] despite having an LDL-C <100 mg/dL. These data highlight that at an A1C >5%, metabolic disease impacts LDL particle remodeling as a function of increasing A1C. MPO identifies a population of people with increased vascular inflammation who are at increased risk for adverse events [20, 36, 37]. While the new CKM guidelines repeatedly discuss the importance of insulin resistance, there are no recommendations to test insulin or how to quantify insulin resistance [9]. The insulin resistance score (IRS) used in this study has been correlated to patients with insulin resistance based on insulin suppression test (IST) using octreotide [38]. IST in paired studies has been shown to have a high degree of correlation to the findings of a euglycemic clamp [39], making the IRS we used a measure of insulin resistance and not based on a secondary consequence of insulin resistance such as HOMA-IR or TG/HDL ratio [21]. Our analysis with IRS shows that as a function of A1C above 5%, there is increasing prevalence of patients at high risk of having insulin resistance long before they develop pre-diabetes (feature of Stage 1 CKM syndrome). Consistent with the IRS score being linked to CKM disease, data shows a high-risk IRS score to be related to risk and prevalence of fatty liver, diabetes, and myocardial infarction [21, 40, 41]. The TG levels identify patients with increasing risk that are unique from other lipid markers in this study,[14] in that it did not decrease with increasing A1C (Figure 2).

Together, these 4 markers demonstrate that 50% of patients have cardiometabolic disease by the time they have prediabetes (A1C of 5.7%). These 4 markers are infrequently redundant (Figure 4A), define unique features of the pathophysiology of cardiometabolic disease, and indicate that patients develop different pathological features of cardiometabolic disease within so-called “normal glucose tolerance”. We demonstrate that people can be identified early in their development of cardiometabolic disease, allowing better patient phenotyping and more appropriate risk stratification within the guideline call to action for LDL-C lowering for prevention [6].

Limitations

This study is limited due to lack of clinical data and follow-up of this patient cohort. However, despite the lack of clinical data, the study shows that at an A1C of 5% there is a progression of the presence of cardiometabolic disease based on blood-based biomarkers. These data are consistent with imaging studies that have shown the correlation of A1C and atherosclerotic burden in otherwise healthy individuals, and offers an accessible blood based biomarker strategy for the quantification of cardiometabolic disease. Future studies with clinical data sets

will allow the assessment of these early sequelae of cardiometabolic disease and long-term clinical outcomes

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Figure Legends

Figure 1: Distribution of A1C for 127,141 patients that had an A1C and apoB simultaneously measured through the national laboratory information system of the Quest Center for Excellence for Cardiometabolic Testing at Cleveland HeartLab in 2021 and 2022. Data are presented in 0.1% increments of A1C.

Figure 2: Distribution of lipid and apoB levels and patient percentages with elevated biomarkers, risks, and apoB-LDL discordance according to HbA1c for the total cohort: (A) non-HDL-C, LDL-C, apoB, and HDL-C levels, (B) the percentage of patients with elevated non-HDL-C, LDL-C and apoB levels based on risk cutoffs, (C) the percentage of patients who had apoB-LDL-C discordance, (D) average TG levels, (E) Percentage of patients with hypertriglyceridemia, (F) the percentage of patients who with apoB-LDL-C discordance that also had hypertriglyceridemia. Data are presented in 0.1% increments of A1C.

Figure 3: Inflammatory biomarkers MPO and IRS a function of A1C in a subcohort of 10,758 patients who had these measures simultaneously with A1C and apoB (A) the percentage of patients that had an elevated MPO defined as greater than 480 pmol/L and (B) Percentage of patients with an elevated IRS defined as >66%. Data are presented in 0.1% increments of A1C.

Figure 4: Four cardiometabolic biomarkers as a function of A1C in the subcohort in which all were simultaneously measured (A) the percentage of patients that had 1 (dark grey), 2 (light grey) or 3 (black) markers elevated, (B) the percentage of patients with elevated apoB-LDL-C discordance (ApoB-LDL Disc) (white), MPO (light grey), IRS (black) or TG (black with dashed line), and (C) the percentage of patients with at least one marker elevated. Data are presented in 0.1% increments of A1C.

Figure 1

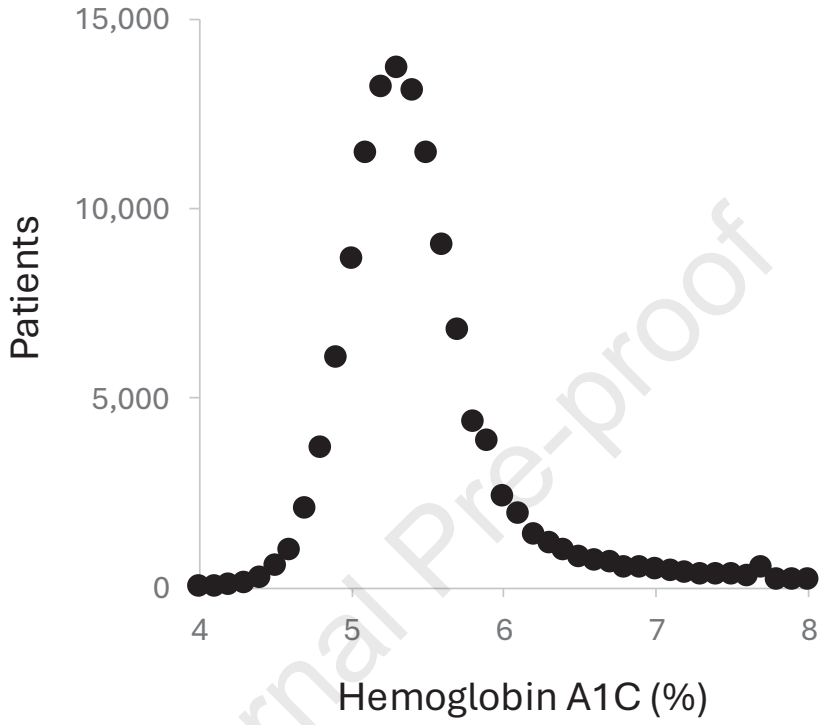


Figure 2

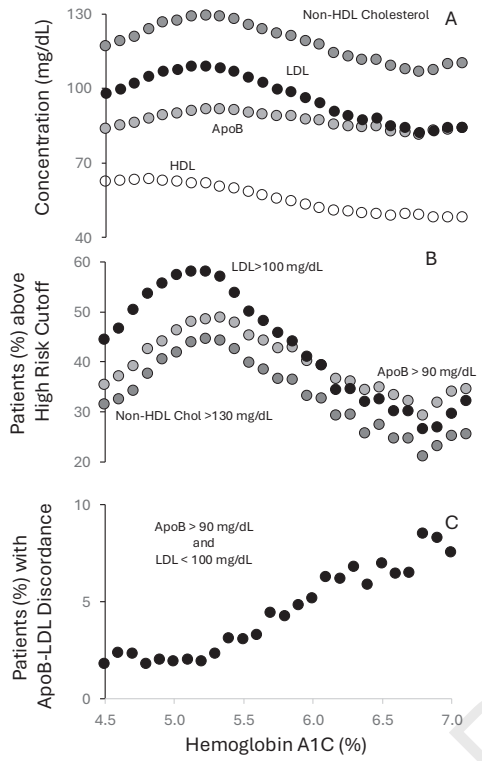


Figure 2

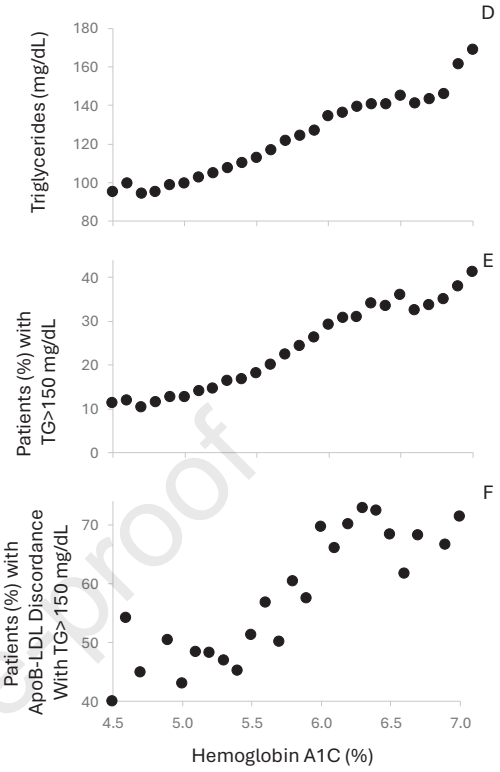


Figure 3

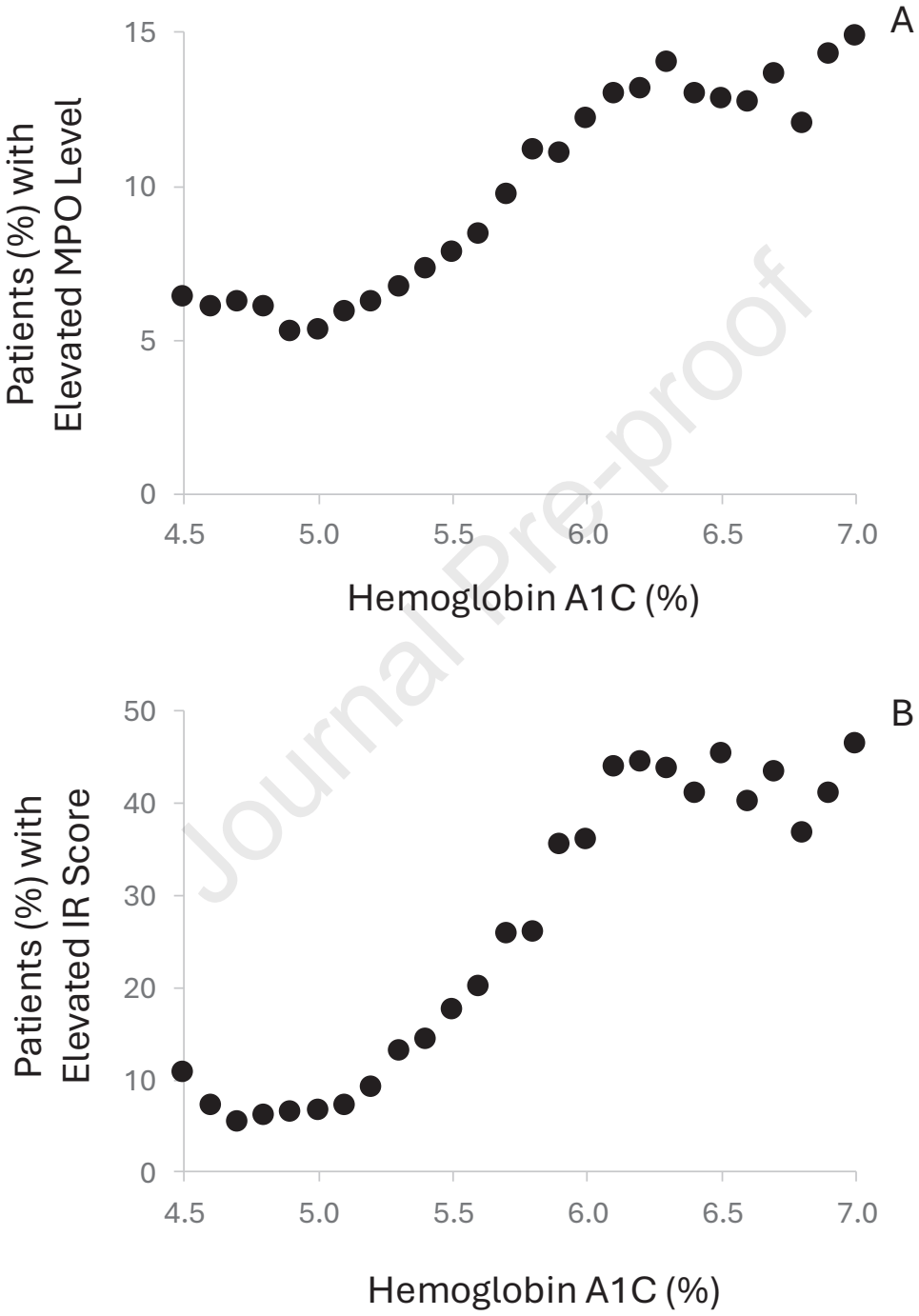
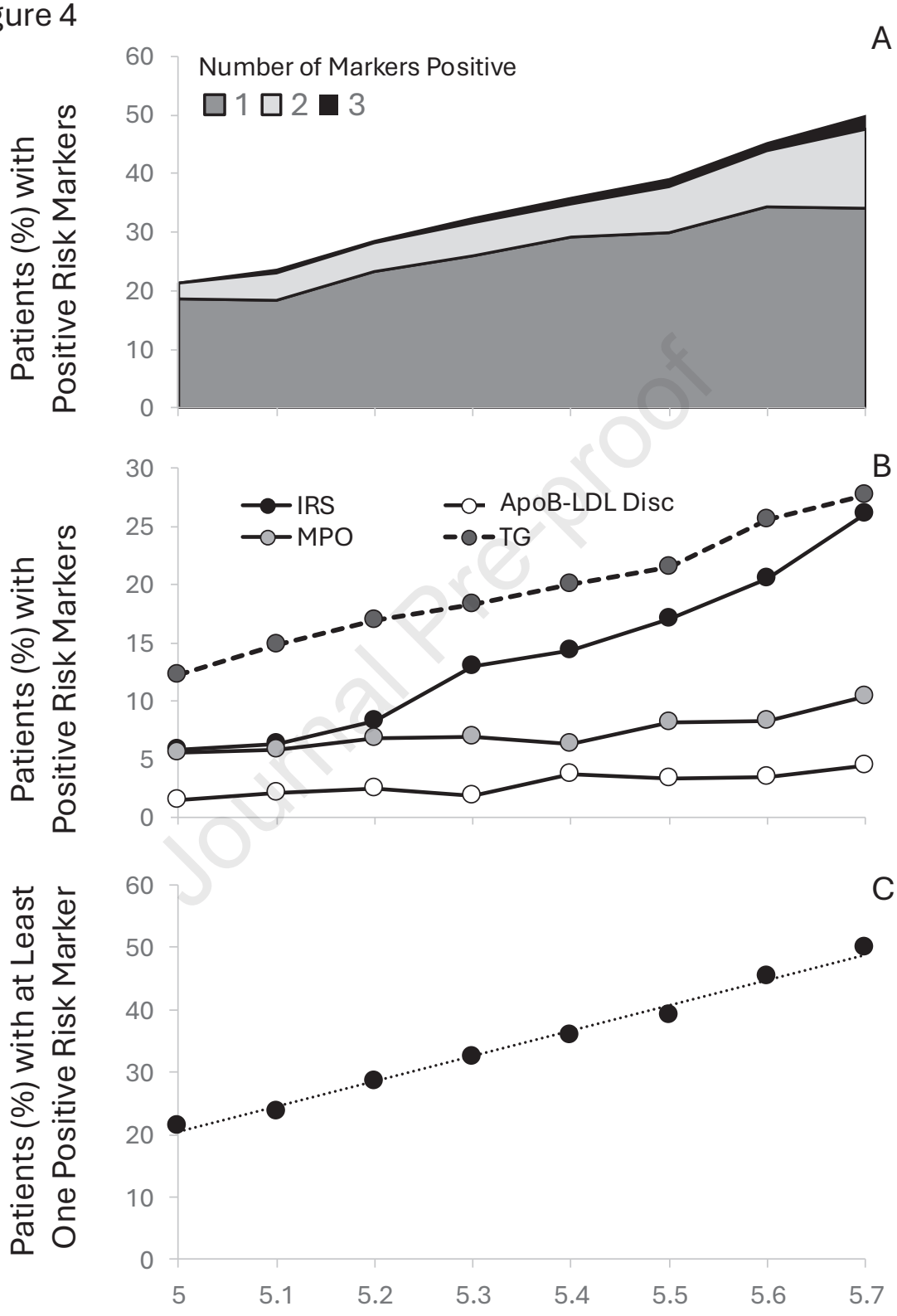


Figure 4



Teaching Points:

- Beginning at an A1C of 5%, there is an increasing prevalence of four modifiable blood-based biomarkers that reflect different properties of cardiometabolic disease: hypertriglyceridemia, vascular inflammation, insulin resistance and apoB-LDL discordance as a function of A1C.
- The abnormal markers are infrequently redundant, and that most persons had a single abnormal biomarker, and no person had all four biomarkers elevated.
- These data demonstrate that individual persons develop different pathological features of cardiometabolic disease within the normal range of A1C offering the opportunity for early risk factor modification.
- Using these 4 measures of cardiometabolic disease, for every increase of 0.1% of A1C between 5% and 5.7%, 4% additional persons demonstrate increasing risk of cardiometabolic disease.

Clinical Relevance:

Cardiometabolic disease is initially a condition of lifestyle. Early recognition of its presence, potentially years before diagnosis of prediabetes, can encourage persons to modify lifestyle to prevent or delay the development of diabetes or loss of end-organ function, as well as identify patients who may benefit from early medical intervention.

Conflicts of Interest:
Marc S. Penn, MD, PhD, FACC – Paid consultant for Quest Diagnostics, Inc. with no equity interest.

Trisha B. Winchester, PhD, Ayorkor Koney, Maeson S. Latsko, PhD, Sanjay B. Dixit, DO and Mouris Saghir, PhD, are employees of Quest Diagnostics, Inc, and as such receive salary and in some cases equity in the company.

Robert H. Eckel, MD and John Saghir – No conflicts of interest to disclose

Contributions
MS, MSP, TBW – Conceived of study
AK, MSP, TBW, MSL, SBJ – Obtained, reviewed and finalized data
JS, MS, MSP, RHE, SBJ – Data analyses and interpretation
JS, MSL, MSP, RHE, SBJ – Manuscript preparation
MSP – Wrote the first draft of the manuscript
All Authors – Manuscript review and finalization

MSP is the guarantor of this work and, as such, had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis

The datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.