Adiposity, circulating metabolic markers, and risk of cardiometabolic multimorbidity

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To the Editor: Adiposity is a prominent global health issue, imposing a considerable burden on cardiometabolic diseases (CMDs, including cardiovascular diseases [CVDs] and diabetes). Beyond the focus on one single CMD, there has been a growing emphasis on their co-occurrence, termed cardiometabolic multimorbidity (CMM). The rising prevalence of CMM poses substantial risks to both individuals and healthcare systems. Notably, the prevalence of CMM has increased from 9% to 14% in the United States between 1999 and 2018, whereas in China, it has nearly tripled, from 2% to 6%, between 2010 and 2016.[1,2]

Prospective studies have linked adiposity to CMM risk. In a meta-analysis of over 120 thousand adults from the United States and Europe, obesity classes I (body mass index [BMI] 30.0–34.9 kg/m^2) and II-III (BMI ≥35.0 kg/m^2) were associated with 4.5 and 14.5 times higher CMM risks, respectively, compared to those of healthy weight (BMI 20.0–24.9 kg/m^2).[3] However, the underlying mechanism between adiposity and CMM remains unclear. Metabolomics offers a unique opportunity to elucidate potential pathways that may mediate the association between adiposity and CMM.

In a case-control study nested within the China Kadoorie Biobank (CKB) cohort, we aimed to investigate: (1) the associations of adiposity with metabolic markers measured by nuclear magnetic resonance (NMR) platform; (2) the associations of these metabolic markers with the risk of CMM; and (3) the potential mediating role of metabolic markers between adiposity and CMM. In addition, we compared the findings for CMM with those for atherosclerotic cardiovascular disease (ASCVD) to elucidate shared pathways.

The CKB study included 512,724 adults aged 30–79 from 10 regions in China, with ethical approvals from Peking University Institutional Review Board (No. IRB00001052–20040) and informed consent. Data collection involved demographic surveys and physical measurements. A nested case-control design identified CMM cases through extended follow-up and defined them by the occurrence of CMD. Adiposity was assessed via BMI and waist circumference (WC), while metabolomics measurements involved targeted NMR analysis of non-fasting plasma samples for 225 metabolic markers.

The study was based on a case-control design nested in CKB, which comprised 3396 CVD cases and 1377 controls, excluding those with prior coronary heart disease (CHD), stroke, or cancer as of January 1, 2015 (median follow-up, 8.7 years). After excluding 315 participants with diabetes, 4458 individuals were analyzed. Cases were coded by International Classification of Disease (ICD)-10 codes for hemorrhagic (I61, I69.1) and ischemic strokes (I63, I69.3) and CHD (I20-I25). We extended follow-up to December 31, 2018 and defined CMM as having two or three of CHD, stroke (hemorrhagic or ischemic), and diabetes (E10-14). Statistical analyses included linear and logistic regression, with adjustments for various confounding factors, and mediation analysis to explore

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the roles of metabolic markers. Sensitivity analyses tested robustness through different CMM definitions and adiposity cut-offs.

The study included 4458 participants with a mean age of 47 ± 8 years, comprising 50.5% females. During follow-up, 259 individuals developed CMM, while 1170 showed no CMD. The overall mean BMI was 23.9 ± 3.5 kg/m^2, and the mean WC was 81.0 ± 10.0 cm. Participants categorized by BMI exhibited significant differences in baseline characteristics, with those having higher BMI also demonstrating increased blood pressure, plasma glucose levels, and a family history of diabetes or CVD. Detailed baseline characteristics are further outlined in Supplementary Table 1, http://links.lww.com/CM9/C387.

Among 225 metabolic markers evaluated, 206 were significantly associated with BMI or WC after adjusting for false discovery rate (FDR) (P <0.05, Supplementary Table 2, http://links.lww.com/CM9/C387). A strong correlation (r = 0.99, P <0.01) was found between metabolic markers related to BMI and WC [Supplementary Figure 1, http://links.lww.com/CM9/C387]. Higher BMI was positively correlated with concentrations of very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), and low-density lipoproteins (LDLs), while inversely related to high-density lipoproteins (HDLs), excluding medium HDL. Similar patterns were observed for cholesterol within these lipoproteins, with triglycerides in nearly all lipoproteins, except large HDL, positively associated with BMI. In addition, BMI positively correlated with apolipoprotein B and the ratio of apolipoprotein B to apolipoprotein A1, while being inversely related to apolipoprotein A1. Specific amino acids like alanine and branched-chain amino acids (BCAAs) were positively associated with BMI, whereas glutamine showed an inverse relationship. Moreover, several glycolysis-related markers, ketone bodies, and fluid balance markers were positively associated with BMI, and total fatty acid concentration increased with BMI, though the ratios of fatty acids to total were generally lower, except for omega-3 and monounsaturated fatty acids.

Out of 225 metabolic markers, 103 were linked to ASCVD, while 141 were associated with CMM [Supplementary Table 3, http://links.lww.com/CM9/C387]. The strongest positive associations with ASCVD included glycoprotein acetyls (GlycA) and specific lipoprotein ratios, with odds ratios (ORs) ranging from 1.20 to 1.32 for each standard deviation increase. For CMM, glucose and lipid ratios in VLDL exhibited even stronger associations, with ORs between 1.72 and 1.75. Notably, specific amino acids, including BCAAs, aromatic amino acids (AAAs), alanine, and histidine, were positively associated with CMM, but not with ASCVD.

Over 100 metabolic markers showed significant associations with both adiposity and disease outcomes, predominantly lipids, along with glucose and specific amino acids [Supplementary Figure 2A, Supplementary Tables 2 and 3, http://links.lww.com/CM9/C387]. Mediation analyses indicated that the effects of adiposity on ASCVD and CMM [Supplementary Table 4, http://links.lww.com/CM9/C387] were partly mediated by these metabolic markers, with indirect effects stronger for CMM (OR = 1.80 for overall adiposity; 1.71 for central adiposity) [Supplementary Figure 2B, http://links.lww.com/CM9/C387] than for ASCVD (OR = 1.20 for overall adiposity; 1.16 for central adiposity). Principal components from these metabolic markers accounted for 29.8% of the total effect of BMI on ASCVD and 55.4% for CMM. For WC, the mediation effects were slightly reduced.

Sensitivity analyses [Supplementary Figures 3–8, http://links.lww.com/CM9/C387] confirmed the robustness of the main findings, showing minimal impact from different definitions of CMM. Comparisons of results in fasting versus non-fasting samples revealed consistent associations with some variations in confidence intervals, indicating possible power limitations in fasting samples. Notably, glutamine emerged as significantly associated with reduced CMM risk in fasting samples, highlighting the complexity of these metabolic interactions.

We discovered that adiposity correlates with numerous metabolic disturbances. Notably, several metabolic markers linked to BMI—such as lipids, amino acids, hexose, and inflammatory markers—mediated approximately half of the total effect of BMI on the risk of CMM. Our findings indicate a stronger association between BMI and CMM compared to ASCVD, with metabolic markers accounting for a larger proportion of this effect. Shared BMI-associated markers between ASCVD and CMM included VLDL and HDL particles, triglycerides, fatty acids, glucose, and GlycA. Interestingly, amino acids were significantly associated with CMM but not with ASCVD.

Although few studies have explored the relationship between NMR-based metabolites and adiposity, most previous research on the metabolic signature of adiposity used mass spectrometry metabolomics. Our study aligns well with earlier findings. For instance, a Finnish study on pregnant women highlighted elevated levels of VLDL subclasses in obese individuals, while large HDL and certain fatty acid ratios were lower. Our research expands this understanding to a broader Chinese adult population, supporting the associations between adiposity and various metabolites, including glycolysis-related compounds and inflammatory markers.[4]

In addition, a randomized controlled trial involving participants with adiposity or diabetes identified early metabolic changes associated with weight loss, further supporting our findings on lipoproteins and other metabolic markers linked to CMM.[5] We specifically noted significant associations of glucose, GlycA, BCAAs, and acetoacetate with CMM risk. This suggests that modifying metabolic profiles through weight loss could reduce CMM risk.

Consistent with previous studies, our results showed that BMI was positively correlated with elevated levels of BCAAs, AAAs, and alanine. Other studies have indicated that these amino acids play a role in insulin resistance and type 2 diabetes (T2D), reinforcing our finding that

they may also influence CMM risk. The metabolic implications of elevated alanine and BCAAs could involve gluconeogenesis and the activation of mechanistic target of rapamycin complex 1 (mTORC1), which may contribute to the pathophysiology linking obesity to insulin resistance and diabetes.

Moreover, we identified GlycA as a key inflammatory metabolic marker associated with both BMI and CMM risk. GlycA serves as an indicator of systemic inflammation, which has been implicated in CMDs. Our findings underscore the significant relationship between GlycA levels and CMM risk. Previous research has also linked inflammatory markers to multimorbidity, suggesting that chronic low-grade inflammation associated with adiposity exacerbates conditions like CMM.

Compared to ASCVD, the metabolic markers showed stronger correlations with CMM, indicating that enhancing metabolic profiles could lead to more significant reductions in CMM risk. Our analysis revealed shared pathways for certain metabolites across both conditions, while highlighting that BCAAs and AAAs were uniquely linked to CMM.

The strengths of our study include robust disease identification and comprehensive metabolic profiling. However, we acknowledge limitations, such as the nested case-control design and reliance on non-fasting samples, which may influence our results. Nonetheless, sensitivity analyses confirmed the consistency of our findings across various definitions of CMM and fasting status.

In conclusion, we identified a distinct metabolic profile related to adiposity that potentially mediates a substantial portion of the risk for CMM in the Chinese population. Reducing BMI and enhancing metabolic health may help lower CMM risk, offering valuable insights for public health initiatives aimed at obesity intervention and CMM management.

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Conflicts of interest

None.

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