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RESPONSE TO LETTER

Comments on "Temporal Relationship Between Visceral Fat and Inflammation, and Their Joint Effect on Cardiometabolic Diseases: Evidence from the China Health and Retirement Longitudinal Study (CHARLS)" [Response to Letter]

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Dear editor

We appreciate the interest and insightful comments from Dr. Zhang regarding our study entitled "Temporal Relationship Between Visceral Fat and Inflammation, and Their Joint Effect on Cardiometabolic Diseases: Evidence from the China Health and Retirement Longitudinal Study. (CHARLS)".[1] In our study, a total of 9559 participants, followed up to 9 years, were included. We found that visceral fat accumulation and inflammation were individually and jointly associated with cardiometabolic disease (CMD) risk. Individuals with concomitant high visceral fat accumulation and elevated inflammation have highest risk of hypertension, diabetes, heart disease, and stroke. There was a biological interaction between visceral fat and inflammation on the incident hypertension and diabetes. In addition, a unidirectional temporal relationship from baseline visceral fat to follow-up inflammation levels was observed. These indicated that combined assessment of both visceral fat and inflammation may improve risk stratification and primary prevention of CMD. We would like to address the valuable points raised by Zhang.[2]

Based on potential mechanisms linking visceral fat and inflammation, this study was conducted to verify one of our hypotheses that there might be a bidirectional relationship between the two factors. A cross-lagged path analysis was performed to evaluate the bidirectional relationship between Chinese visceral adiposity index (CVAI) and high-sensitivity C-reactive protein (hs-CRP), including both directions (visceral fat → inflammation, and inflammation → visceral fat). As shown in Figure 3 (in the original paper), there were temporal relationships from baseline CVAI to follow-up hs-CRP, but not from baseline hs-CRP to follow-up CVAI, indicating a unidirectional relationship. Despite the theoretical possibility that inflammation influences visceral fat accumulation, our study found no statistical evidence for this reverse causal pathway. However, future research should account for potential variations in results due to heterogeneity in populations, disease types, and analytical models. We agree with Dr. Zhang's opinion that other statistical methods can be used to further verify the causal relationship.

As described in the limitation section, we used a hs-CRP threshold of 1mg/L in the primary analyses given the number of groups and sample size, which was lower than that in some previous studies. It is noteworthy that even a low-grade inflammation could increase CMD risk by interacting with visceral fat accumulation. Moreover, the stability of the main results was verified in sensitivity analyses using 1 or 3 as the threshold for hs-CRP, in which similar results were observed (Table S8 in the original paper).

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While both multiplicative and additive interaction analyses evaluate effect modification between exposures, they operate on different scales (ratio or difference), and thus address distinct research questions. Consequently, the results from these two approaches may not always be consistent. As far as we know, additive interaction is more sensitive for assessing biological interactions,[3] and it has more values in public health and clinical decision-making, as it provided quantitative measurement of additional absolute risks.[4] We agree with Dr. Zhang that the effect of visceral fat accumulation and inflammation may not be completely synergistic, which needs to be further explored through more statistical analyses and basic experimental research. Nonetheless, the combined assessment of both visceral fat and inflammation could be used to identify individuals early who are at high risk of hypertension and diabetes.

As mentioned in the original paper, our findings require verification in population from other regions or ethnic backgrounds, as well as in younger individuals, because the included population was composed of middle-aged and elderly people from China. It is noteworthy that similar results regarding the individual effects of visceral adiposity and inflammation on cardiovascular diseases were reported from different populations.[5–9] Future studies from other regions or populations are warranted to explore the combined and interaction effects of visceral fat and inflammation on cardiovascular diseases. In response to Zhang's comments, we have provided the baseline characteristics of the exclusion population and compared them with the inclusion population, based on available data (Table 1). Characteristics of BMI, drinking status, blood pressure, serum creatinine, and hs-CRP were statistically comparable between the two groups of population ($P > 0.05$). The other baseline characteristics showed significant but slight difference, which may mainly due to the relatively large sample size. For instance, there was statistical difference in age between the two groups ($P < 0.001$), but the difference in mean value was only 0.5 years. Similarly, for the fasting plasma glucose, the difference was only 0.1 mmol/L, whereas the P value was 0.004. Although there was higher proportion of cardiometabolic diseases in the inclusion group, the prevalences of hypertension and diabetes of the inclusion population (mainly composed of middle-aged and elderly people) were similar to reports of other nationwide surveys in China.[10,11] In addition, missing

Table 1 Comparison in Baseline Characteristics Between Inclusion and Exclusion Populations

Characteristics	Inclusion (n =9559)	Exclusion (n =8146)	*P*-value	Sample Size for Analysis in Exclusion Group (Number)
Age (years)	59.3 ± 9.6	58.8 ± 10.7	< 0.001	8092
Sex, female, n (%)	5164 (54.0)	4057 (49.9)	< 0.001	8133
Smoking, n (%)	3709 (38.8)	3222 (46.5)	0.045	7998
Drinking, n (%)	3896 (40.8)	3314 (41.5)	0.342	7992
Body mass index (kg/m^2)	23.5 ± 3.9	23.3 ± 3.9	0.393	4062
Waist circumference (cm)	85.3 ± 10.0	84.2 ± 12.6	< 0.001	4208
Systolic blood pressure (mmHg)	130.7 ± 21.6	130 ± 21.5	0.861	4175
Diastolic blood pressure (mmHg)	75.8 ± 12.1	76.2 ± 12.1	0.987	4175
Fasting plasma glucose (mmol/L)	6.1 ± 2.0	6.2 ± 2.3	0.004	2077
Total cholesterol (mmol/L)	5.0 ± 1.0	5.0 ± 1.1	0.019	2081
Triglycerides (mmol/L)	1.16 (0.83–1.69)	1.21 (0.87–1.85)	< 0.001	2097
LDL-C (mmol/L)	3.0 ± 0.9	3.0 ± 0.9	0.636	2082
HDL-C (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	0.759	2103
Serum creatinine (μmol/L)	66.9 (57.9–77.9)	66.7 (57.8–78.7)	0.872	2075
Uric acid (mg/dl)	4.4 ± 1.3	4.6 ± 1.3	0.012	2105
hs-CRP (mg/L)	1.0 (0.6–2.2)	1.0 (0.6–2.3)	0.182	2105
Cardiometabolic diseases at baseline, n (%)				
Hypertension	3907 (40.9)	2678 (33.6)	< 0.001	7978
Diabetes mellitus	1541 (16.1)	695 (8.7)	< 0.001	7942
Heart disease	1394 (14.6)	977 (12.3)	< 0.001	7958
Stroke	294 (3.1)	211 (2.6)	0.149	7994

Notes: Data are presented as the mean ± SD, n (%), or median (interquartile range).
Abbreviations: HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

data may have contributed to the underestimation of the prevalences in the excluded population. We agree with Dr. Zhang that the generalizability of the results should be verified in other populations.

In summary, Dr. Zhang's comments, which focused on the stability and generalizability of our findings, are valuable for improving the current study and instructive for future research. We believe that our study provides a comprehensive insight for understanding the association and potential mechanisms between visceral fat accumulation, inflammation and cardiometabolic diseases. Approaches that simultaneously target adiposity and inflammation should yield greater benefits than targeting each individual risk factor. In addition, future studies focus on the incremental value of CVAI and hs-CRP in risk prediction models would be valuable.

Data Sharing Statement

No new data has been generated for this communication.

Author Contributions

Mengyue Lin – Conceptualization, Formal analysis, Writing – original draft, Writing – Review & Editing; Xuerui Tan – Conceptualization, Data curation, Validation, Writing – Review & Editing; Yequn Chen – Conceptualization, Data curation, Validation, Writing – Review & Editing. All authors agreed to the journal where this communication was submitted, agreed to the final version submitted for publication and agree to be accountable for the contents of this communication.

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Disclosure

The authors declare that they have no competing interests.

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