# Effects of long-term particulate matter exposure on platelet counts in adults of Northeast China

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**Research**

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# Abstract

Associations between air pollution exposure and platelet counts have been inconsistent in previous studies, and there have been few studies of effects of long-term exposure in Asian populations. We explored the associations between long-term $PM_{2.5}$ (particulate matter < 2.5 μm) exposure and platelet counts using a prospective cohort study in Northeast China. We used a logistic regression model to analyze the effects of different $PM_{2.5}$ increments and platelet count elevation. Mixed linear models were used to analyze the association between $PM_{2.5}$ concentration and platelet counts. Interaction and stratified analyses were also conducted. Results showed that every 1 $\mu g/m^3$ increment of $PM_{2.5}$ exposure was associated with 0.29% (95%CI: 0.25–0.32%) increase in platelet counts and 10% (95%CI: 8–12%) higher risk of platelet elevation. Effects of long-term $PM_{2.5}$ exposure on platelet elevation were stronger in male participants, of Han ethnicity, and without diabetes. Our findings add more evidence to the potential biological mechanisms responsible for the effect of air pollution exposure on cardiovascular disease.


# 1. Introduction

Previous studies showed that acute and long-term exposure to air pollution (especially particulate matter < 2.5 μm, i.e. $PM_{2.5}$) were both associated with higher morbidity and mortality of cardiovascular diseases[1, 2]. Studies in animals also showed that exposure to $PM_{2.5}$ increases blood coagulability, which accelerates atherosclerosis progression and results in vascular diseases[3, 4]. Underlying mechanisms relating air pollution exposure to cardiovascular diseases include platelet activation, oxidative stress and interplay between interleukin-6 and tissue factors[5, 6], of which increased platelet count is associated with increased blood coagulability and cardiovascular disease mortality[7, 8]. Previous epidemiological studies on associations between air pollution and platelet counts gave inconsistent results and mainly concentrated on short-term exposure assessment[9, 10]. Studies of the effects of long-term air pollution exposure on platelet counts in large populations are limited[11], especially in Asian populations.

In this study, we aim to explore the associations between long-term $PM_{2.5}$ exposure and platelet counts in adults in Northeast China based on a large cohort population. Results may provide more evidence of associations between long-term air pollution exposure and cardiovascular diseases.

# 2. Materials And Methods

# 2.1. Study participants

Participants in this study came from a large prospective natural population cohort in Northeast China, which is supported by the National K&D Project of China. The cohort consisted of four sub-cohorts: adults in city and county, maternal-children, special job exposures and health management. There were 30,000 adults in city and country included in this study. All participants responded to questionnaires and received physical examinations and blood tests. We excluded participants who did not provide detailed

living addresses or complete blood platelet count tests, and 25,355 participants were included in the final analysis. The protocol of this study was approved by the Ethics Committee of the Shengjing Hospital of China Medical University (No. 2017PS190K).

## 2.2. Air pollution exposure assessment

We use two-year average $PM_{2.5}$ concentration for the living address of each participant as the measure of long-term air pollution exposure. All participants were from Liaoning Province. Annual land use regression model based on 78 national monitoring stations were used to construct land use regression model and predict air pollution exposure, the method of which was described in detail in our previous study[12]. Addresses of each participant were transformed into latitude and longitude data and imported into ArcGIS 10.3. Then we estimated average $PM_{2.5}$ concentration for the year of the blood test and the previous year separately for each participant. The two-year average $PM_{2.5}$ concentration value was used as long-term ambient $PM_{2.5}$ exposure.

## 2.3. Platelet counts test

All blood routine examinations were conducted in the Laboratory Department in Shengjing Hospital of China Medical University. Platelet count was included in the routine blood examination. The normal reference range of platelet counts is $100 \times 10^9$ to $350 \times 10^9$/ml. Tests of fasting blood-glucose and blood lipids were also included.

## 2.4. Other factors involved

Age, gender, race, income, status of education, smoking and alcohol drinking, indoor decoration in the previous five years, activity time per week, white blood cell (WBC) counts and presence of hypertension, diabetes, hyperlipemia and heart disease were included in the final analysis due to their confounding effects on the association between long-term $PM_{2.5}$ exposure and platelet counts[13]. Race was divided into Han, Manchu and others. Education level was divided into three categories according to education duration: <6, 6–12 and > 12 years. Smoking and alcohol drinking status were divided into current, ever and never. Activity degree was divided into three categories according to the physical exercise duration per week: <1, 1–2 and > 2 h. Hypertension was defined as average systolic pressure of three separate measures over 140 mmHg or average diastolic pressure of three separate measures over 90 mmHg. Diabetes was defined as fasting blood-glucose over 7 mmol/L. Heart disease was self-reported in the questionnaire. Hyperlipemia was defined as total cholesterol over 6.2 mmol/L, low-density lipid cholesterol over 4.1 mmol/L, triglyceride over 5.2 mmol/L or high-density lipid cholesterol below 1 mmol/L.

## 2.5. Statistical analysis

We defined elevated platelet count as a platelet count over the 90th percentile. Continuous variables are presented as least square means with 95% confidence intervals (CIs), and categorical variables are presented as total counts with percentages. Variance analyses and $c^2$ tests were conducted between

each variable and platelet elevation. We used different logistic models to examine the associations between every 1 μg/$m^3$ increment of $PM_{2.5}$ exposure and elevated platelet count. Model 1 was used to calculate crude odds ratios (ORs). Model 2 was adjusted for age, gender, race, education, income and body mass index (BMI). Model 3 was further adjusted for status of smoking and alcohol drinking, decoration in the previous five years, hypertension, diabetes, heart disease, hyperlipemia, activity per week and WBC counts. We also divided $PM_{2.5}$ exposure into four categories according to quartile and used the first quartile as a reference to calculate the effects of $PM_{2.5}$ exposure in other quartiles on platelet elevation. Effects of interactions of $PM_{2.5}$ exposure with other involved factors on platelet elevation were examined separately. Further stratified analysis was conducted based on significant interactions of confounding factors with $PM_{2.5}$ exposure. Several sensitivity analyses were conducted, and mixed linear analyses were used to examine the linear associations between $PM_{2.5}$ exposure and log-transformed platelet counts. Elevated platelet count was defined as a platelet count over the 75th percentile for the logistic analysis. All analyses were conducted using SAS version 9.4 and SPSS version 25.0.

# 3. Results

General characteristics of the study participants are shown in Table 1. Among the 25,355 participants, 9.7% (n = 2467) were categorized as having platelet elevation. There were significant effects on platelet elevation of age, gender, race, education level, status of smoking and alcohol drinking, indoor decoration, activity per week, WBC counts and having hypertension, heart disease or hyperlipemia.

Table 1
General characteristics of the study participants.

| Characteristics | | Platelet counts | | P-value |
|---|---|---|---|---|
| | | ≤P90[a] (n = 22,888) | >P90[b] (n = 2467) | |
| Age, years | | 54.2 (54.1,54.4)[c] | 51 (50.6,51.5) | < 0.0001[d] |
| Gender, n[e] (%) | Male | 8126 (35.5)[f] | 534 (21.7) | < 0.0001 [g] |
| | Female | 14761(64.5) | 1932(78.3) | |
| Race, n (%) | Han | 14571(63.7) | 1622(65.7) | 0.006 |
| | Manchu | 8287(36.2) | 837(33.9) | |
| | Other | 30(0.1) | 8(0.3) | |
| Income (10,000 Yuan) | | 31.7(13.7,49.8) | 5.8(5.6,6) | 0.355 |
| BMI, kg/m$^2$ | | 31(25.6,36.4) | 28.4(24.6,32.2) | 0.763 |
| Education, n (%) | 0–6 years | 5551(24.3) | 497(20.1) | < 0.0001 |
| | 7–12 years | 13602(59.4) | 1458(59.1) | |
| | > 12 years | 3735(16.3) | 512(20.8) | |
| Smoke, n(%) | Current | 3597(15.7) | 337(13.7) | < 0.0001 |
| | Ever | 1016(4.4) | 64(2.6) | |
| | Never | 18275(79.8) | 2066(83.7) | |
| Alcohol, n(%) | Current | 3996(17.5) | 361(14.6) | < 0.0001 |
| | Ever | 362(1.6) | 31(1.3) | |
| | Never | 18530(81) | 2075(84.1) | |
| Decoration, n(%) | No | 18958(82.8) | 1934(78.5) | < 0.0001 |
| | Yes | 3925(17.2) | 531(21.5) | |
| Hypertension, n(%) | No | 14425(63) | 1640(66.5) | 0.001 |
| | Yes | 8463(37) | 827(33.5) | |
| Diabetes, n(%) | No | 19906(87) | 2161(87.6) | 0.38 |
| | Yes | 2982(13) | 306(12.4) | |
| Heart disease, n(%) | No | 21390(93.5) | 2329(94.4) | 0.068 |
| | Yes | 1498(6.5) | 138(5.6) | |

| Characteristics | | Platelet counts | | P-value |
|---|---|---|---|---|
| | | ≤P90[a] (n = 22,888) | >P90[b] (n = 2467) | |
| Activity, n(%) | < 1 h/week | 10768(47) | 1186(48.1) | < 0.0001 |
| | 1–2 h/week | 2341(10.2) | 316(12.8) | |
| | > 2 h/week | 9779(42.7) | 965(39.1) | |
| Hyperlipemia, n(%) | No | 18534(81) | 1805(73.2) | < 0.0001 |
| | Yes | 4354(19) | 662(26.8) | |
| White blood cell count ($10^9$/ml) | | 6.2(6.2,6.3) | 7.2(7.1,7.2) | < 0.0001 |
| $PM_{2.5}$ exposure (μg/$m^3$) | | 36.8(36.7,36.8) | 37.7(37.5,37.9) | < 0.0001 |

a, ≤ 90th percentile; b, > 90th percentile; c, least square means with 95% CI intervals – applies to all such values; d, P-values of variance analyses – applies to all such values; e, number of participants; f, total counts with percentages – applies to all such values; g, P-values of $c^2$ tests – applies to all such values.

Average $PM_{2.5}$ exposure of all participants was 37.25 μg/$m^3$ with a significant difference between participants with elevated platelet counts and those without. Figure 1 shows the distributions of participant locations and variation in $PM_{2.5}$ exposure across the whole study area.

The associations between $PM_{2.5}$ exposure and 90th percentile platelet elevations remained stable after adjusting for all possible confounders (Table 2). When $PM_{2.5}$ was treated as a continuous variable, the OR between every 1 μg/$m^3$ increment of $PM_{2.5}$ exposure and platelet elevation was 1.1 (95%CI: 1.08–1.12). When $PM_{2.5}$ was treated as a categorical factor, compared with participants in the first quartile, those in the third (OR = 1.28, 95%CI: 1.08–1.52) and fourth (OR = 2.18, 95%CI: 1.83–2.60) quartiles were more likely to have elevated platelet counts.

Table 2
Effects of $PM_{2.5}$ exposure on 90th percentile platelet elevation.

| $PM_{2.5}$ | OR (95%CI) | | | | | |
|---|---|---|---|---|---|---|
| | Model 1 | P-value | Model 2 | P-value | Model 3 | P-value |
| 1 μg/$m^3$ increment | 1.06 (1.05,1.08) | < 0.0001 | 1.11(1.09,1.12) | < 0.0001 | 1.1(1.08,1.12) | < 0.0001 |
| 1st quartile | Ref | | Ref | | Ref | |
| 2st quartile | 0.88(0.77,1.0) | 0.05 | 1.07(0.92,1.25) | 0.37 | 1.1(0.94,1.29) | 0.24 |
| 3rd quartile | 1.02(0.9,1.16) | 0.73 | 1.31(1.11,1.55) | 0.00 | 1.28(1.08,1.52) | 0.01 |
| 4st quartile | 1.84(1.64,2.05) | < 0.0001 | 2.21(1.88,2.59) | < 0.0001 | 2.18(1.83,2.6) | < 0.0001 |
| P-value for trend | < 0.0001 | | < 0.0001 | | < 0.0001 | |

Model 1, crude model; Model 2, adjusted for age, gender, race, education, income and BMI; Model 3, further adjusted for status of smoking and alcohol drinking, decoration in the previous five years, hypertension, diabetes, heart disease, hyperlipemia, activity per week and white blood cell counts.1st quartile, $PM_{2.5} \leq$ 25th percentile; 2nd quartile, 25th percentile < $PM_{2.5} \leq$50th percentile; 3rd quartile, 50th percentile < $PM_{2.5} \leq$75th percentile; 4th quartile, $PM_{2.5}$ > 75th percentile.

Model 3 showed significant interactions of $PM_{2.5}$ exposure with gender (P < 0.01), race (P < 0.0001) and diabetes status (P < 0.001). Figure 2 shows the stratified analysis results according to gender (male and female), race (Han and Manchu) and diabetes (yes and no). Males were more likely to have platelet elevation after long-term $PM_{2.5}$ exposure compared with females. Those of Han ethnicity were more likely to have platelet elevation compared with Manchu ethnicity. Participants without diabetes were more likely to have platelet elevation after long-term $PM_{2.5}$ exposure.

Sensitivity analysis results are shown in Supplemental Tables 1 and 2. Analysis results for the mixed linear model between long-term $PM_{2.5}$ exposure and platelet counts showed that every 1 μg/$m^3$ increment of $PM_{2.5}$ exposure was associated with 0.29% (95%CI: 0.25–0.32%) increase in platelet counts; and effects of $PM_{2.5}$ exposure were more evident in participants who were male, of Han ethnicity and without diabetes (Supplemental Table 1). Using the 75th percentile as the cut-off to define elevated platelet counts gave similar results (Supplemental Table 2) to those for the 90th percentile.

# 4. Discussion

To our knowledge, this is the first cohort study in mainland China focusing on the association between long-term air pollution exposure and platelet counts. We found that long-term $PM_{2.5}$ exposure was associated with elevated platelet counts – every 1 μg/$m^3$ increment of $PM_{2.5}$ exposure was associated with 0.29% increase in platelet counts and 10% higher risk of platelet elevation. Gender, race and diabetes status might interact with long-term $PM_{2.5}$ exposure in regard to platelet counts. Our findings add more evidence to determining the potential biological mechanisms relating air pollution exposure to cardiovascular disease.

Results of this study are similar to those of some previous studies focusing on the associations between short-term PM exposure and platelet activation (platelet count elevation or platelet aggregation)[14, 15, 16] in Europe and China. In a large cohort study of Taiwanese adults, long-term $PM_{2.5}$ exposure was associated with elevated platelet counts, but with a weaker effect than in our study, possibly because the Taiwanese study population was generally younger than in our study[17]. A prospective cohort study of German adults also found similar results, with every 2.4 μg/$m^3$ increment of $PM_{2.5}$ exposure associated with an adjusted increase of 2.3% in platelet counts[18]. Animal experiments also showed that repeat dose exposure of $PM_{2.5}$ triggered disseminated intravascular coagulation in Sprague Dawley rats with elevated platelet counts[19].

We also found significant differences in the effects of long-term $PM_{2.5}$ exposure on platelet elevation related to gender, race and diabetes of participants. Stronger associations between $PM_{2.5}$ exposure and platelet elevation were found for male participants, similar to previous studies[20] – the biological mechanisms responsible might be the effects of different hormone levels in men and women, which may interact with chemicals in $PM_{2.5}$ [21] but more studies are required. Significant differences in platelet parameters as well as related risk factors have been found for European and Asian countries[22], but race-related effects on platelet counts following long-term $PM_{2.5}$ exposure have seldom been mentioned. There were considerable proportions of Han and Manchu ethnicities among participants in our study. Research has revealed that frequencies of human platelet alloantigen alleles differ among Chinese ethnic groups[23] and associated risk factors differ among different races[24], which might explain some of the effects of race on platelet counts with $PM_{2.5}$ exposure. Previous studies reported that the effect of ultra-fine particulates on thrombosis was significantly attenuated in diabetic subjects taking aspirin[25, 26], possibly explaining our results of weaker effects of long-term $PM_{2.5}$ exposure on platelet elevation in participants with diabetes. We found no significant effects of other cardiovascular-related risk factors such as age and BMI[27], possibly because the average age of participants was over 40 years and the younger sub-group was relatively small.

The biological pathway of platelet activation following $PM_{2.5}$ exposure remains unclear. A previous study showed that $PM_{2.5}$ exposure increased the methylation levels of CpG sites, with the function related to platelet activation, inflammation and oxidative stress[14]. Furthermore, more oxidative stress after $PM_{2.5}$ exposure reflected in an increased level of reactive oxygen species, which can also promote platelet

activation, has been hypothesized as a possible mechanism[14]. Previous studies showed PM exposure was also associated with changes in fibrinogen levels, extracellular vesical release and miRNA content[29]; however, the biological pathway related to platelet activation or pro-thrombosis requires further research.

This is the first cohort study in Northeast China to study the association between long-term $PM_{2.5}$ exposure and platelet counts. The large number of participants gave stable results, as shown by our sensitivity analysis. The abundant information from questionnaire and blood tests gave an assessment of a wide range of potential confounders, which allowed us to better characterize the associations and find new modifiers. Although this was a multi-center cohort study, all tests of platelet counts were from one laboratory, thus there was no heterogeneity in outcome definition, making our results reliable. However, there were some limitations in this study. First, although previous study demonstrated the predictive value of platelet counts for thrombosis and cardiovascular diseases[30], using platelet counts alone to represent coagulation might limit the specificity blood coagulation assessment and future study should include more specific biomarkers. However, low test cost and easy availability make platelet counts more suitable for large-scale epidemiological studies compared to other biomarkers. Second, participants in our cohort were comparatively older than in previous studies, which might have resulted in a stronger correlation between $PM_{2.5}$ exposure and platelet elevation. Third, $PM_{2.5}$ level was comparatively higher than those reported in other countries, which might also explain the stronger correlation between $PM_{2.5}$ exposure and platelet elevation in our study, although this allowed us to investigate health effects of $PM_{2.5}$ exposure across a wider range.

## 5. Conclusion

We explored the associations between long-term $PM_{2.5}$ exposure and platelet counts based on a prospective cohort study in Northeast China. We found long-term $PM_{2.5}$ exposure was associated with elevated platelet count. Gender, race and diabetes status interacted with the effect of long-term $PM_{2.5}$ exposure on platelet counts. Our findings add evidence concerning the potential biological mechanisms responsible for the relationship between air pollution exposure and cardiovascular disease. We recommend more epidemiological study on the interactions of air pollution exposure with race and disease status, and more basic research on the biological pathway of platelet count elevation after air pollution exposure.

## Declarations

# Conflicts of interest

The authors declare that they have no competing financial interests.

# Ethics approval and consent to participate

The protocol of this study was approved by the Institutional Review Board of Shengjing Hospital of China Medical University in 2017 (No. 2017PS190K).

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# Authors' contributions

Zhang Hehua analyzed the data and wrote the paper; Zhao Yuhong designed the study process and reviewed the work.

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# Figures

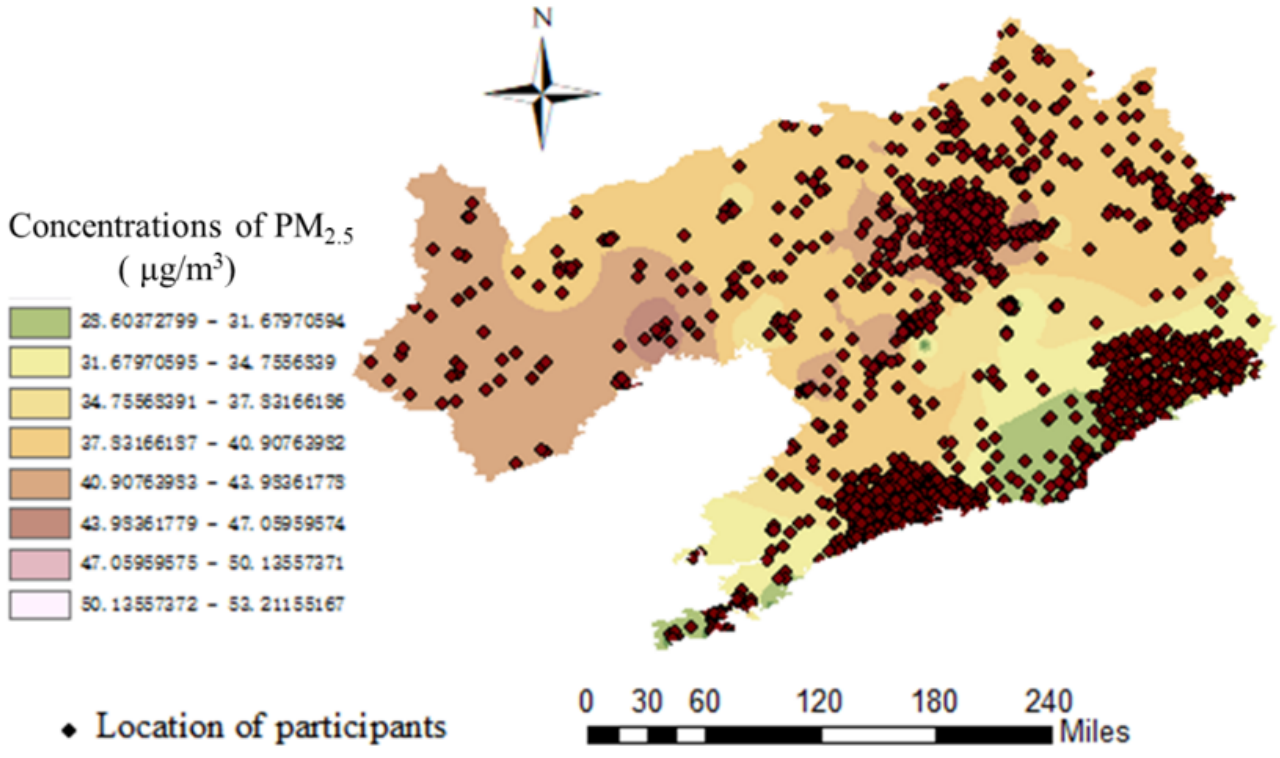

**Figure 1**

Distributions of participants and PM2.5 exposure. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

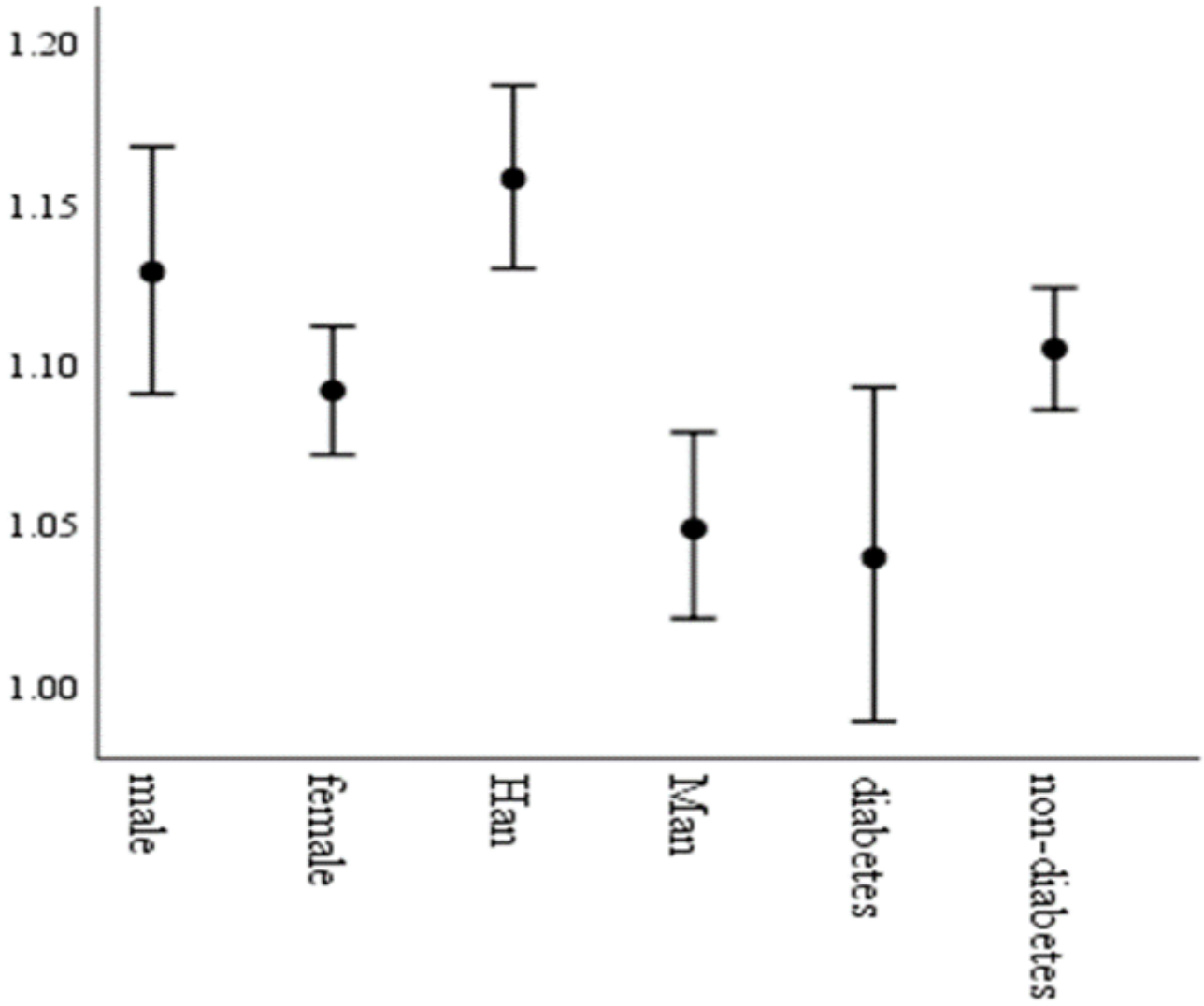


**Figure 2**

Stratified analysis according to gender, race and diabetes.

## Supplementary Files

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