Mean platelet volume (MPV) is a determinant of activation and variability of platelets (PLT). The focus of this study was to investigate MPV values in patients with and without metabolic syndrome (MS). It also evaluated the association between them. There are close connections among MPV, MS, and cardiometabolic risk. We compiled age, body mass index, blood cell counts, MPV, and other data of 59,976 self-reported healthy volunteers (28,428 male, 31,548 female), 24.65% of whom have MS. The mean age of the group was 48.21 years old. The data was grouped by sex and values of data between men and women groups were analyzed by independent sample’s t-test. The relationship between sex and MS was evaluated by chi-square tests. Crude odd ratios of MS between MPV quartiles and 95% confidence intervals were analyzed by binary logistic regression in this study. We found women had higher levels of MPV (10.09 vs. 9.98, \( P < 0.01 \)) and PLT (228.68 vs. 212.11, \( P < 0.01 \)) than men. In females, the prevalence of MS was higher in low MPV group than in high MPV groups. The odds of having MS were significantly lower in higher MPV quartiles compared with MPV Quartile 1 in women (Adjusted OR < 1, \( P < 0.01 \)). This study indicated that MS was inversely associated with MPV in females only.

Metabolic syndrome (MS) means a cluster of cardiometabolic risk factors including elevated blood pressure, central obesity, atherogenic dyslipidemia and impaired glucose metabolism\(^1\).\(^2\). A study reported that 20% of adults in the Western world have MS\(^3\). Getting complete blood count (CBC) is a convenient and affordable way to reveal the hematological status and, can probably provide important information indicating MS. Some studies have demonstrated that the levels of hemoglobin, red blood cell (RBC), white blood cell (WBC), and blood platelet (PLT) were higher in adults with MS\(^4\). Other studies have found a positive correlation between PLT aggregation function and mean platelet volume (MPV)\(^5\),\(^6\). Larger and more reactive PLTs increase the possibility of thrombosis. MPV is associated with a wide variety of diseases such as cardiovascular disease (CVD) and diabetes mellitus (DM)\(^7\). Furthermore, some investigations found MS could predispose people to the development of CVD and DM. These investigations would suggest a high level of MPV as a potential risk factor for MS. But, there are controversies about the associations between MPV and MS. For instance, Aypak et al.\(^8\) showed that patients with MS had a significantly lower MPV level and this, phenomenon only appeared in females. And the volunteers of this investigation were only pre-pubertal children. However, Lee et al.\(^9\) found that MPV in patients with MS was significantly higher compared with the control groups. In addition, gender differences have not been given enough attention through available literature. Therefore, here we aimed to research the association between MPV and MS in different sex group.

1Department of Nuclear Medicine, Tianjin Medical University General Hospital, Tianjin, P. R. China. 2Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital, Tianjin, P. R. China. 3Department of Health Management, Tianjin Medical University General Hospital, Tianjin, P. R. China. Fengxiao Zhao and Ziyu Yan contributed equally. Correspondence and requests for materials should be addressed to Z.M. (email: jamesmencius@163.com)

Received: 28 February 2018
Accepted: 14 September 2018
Published online: 01 October 2018
Results

Characteristics of the participants in different genders. Table 1 showed significant data differences in different genders. Males were older than females. Body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), alanine aminotransferase (ALT), creatinine (Cr), triglycerides (TG), glucose (GLU), WBC, RBC and platelet distribution width (PDW) were significantly higher in males than in females. Total cholesterol (TC), high density lipoprotein (HDL), MPV and PLT were significantly lower in males than in females.

Incidence of MS in different genders by MPV quartiles. Date was grouped by MPV quartiles, and within each MPV quartile MS incidences for females and males were calculated and compared. The same analysis was also done for the overall group. Females with lower MPV were more likely to be afflicted with MS. Males showed significantly higher overall incidence of MS than females (Table 2).

Correlations between MPV and other key variables. MPV displayed significant negative relationships with age, SBP, DBP, Cr, TC, GLU and PLT in both genders. But MPV demonstrated positive relationships with ALT, TG, WBC and RBC in men, as well as ALT and HDL in women (Table 3).

Risks of MS in different MPV quartiles. Binary logistic regression models were conducted to calculate the ORs of MS among MPV quartiles using the lowest MPV quartile as reference for both genders (Table 4). For women, significant risks of MS were demonstrated in low MPV quartiles, with or without adjustment for age and BMI. However, MPV was not a significant indicator in men.

---

Table 1. Population characteristics based on different genders. BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, ALT = alanine aminotransferase, Cr = creatinine, TC = total cholesterol, TG = triglycerides, HDL = high-density lipoprotein cholesterol, GLU = glucose, WBC = leukocyte, RBC = erythrocyte, PDW = platelet distribution width, MPV = mean platelet volume, PLT = platelet. *P < 0.05, **P < 0.01 (analyzed by independent sample’s t test).

| Characteristic         | Total   | Male   | Female  | T value |
|------------------------|---------|--------|---------|---------|
| Age (years)            | 48.21± 12.87 | 49.08± 12.61 | 47.43± 13.03 | 15.711** |
| Weight (kg)            | 67.99± 12.30 | 75.69± 10.71 | 61.05± 9.08 | 181.087** |
| BMI (kg/m²)            | 24.75± 3.44 | 25.64± 3.18 | 23.95± 3.47 | 61.824**  |
| Waist (cm)             | 83.71± 10.59 | 89.11± 8.89 | 78.84± 9.60 | 135.707** |
| SBP (mmHg)             | 123.06± 17.62 | 125.35± 16.72 | 120.99± 18.16 | 30.546**  |
| DBP (mmHg)             | 77.35± 11.05 | 80.35± 11.13 | 74.65± 10.24 | 65.366**  |
| ALT (U/L)              | 21.47± 12.53 | 24.92± 13.52 | 18.36± 10.64 | 66.428**  |
| Cr (µmol/L)            | 68.81± 14.22 | 78.82± 11.59 | 59.78± 9.56  | 220.202** |
| TC (mmol/L)            | 5.15± 0.98  | 5.08± 0.92  | 5.21± 1.03  | −16.350** |
| TG (mmol/L)            | 1.42± 0.84  | 1.61± 0.91  | 1.24± 0.72  | 55.660**  |
| HDL (mmol/L)           | 1.45± 0.36  | 1.31± 0.32  | 1.57± 0.36  | −91.207** |
| GLU (mmol/L)           | 5.13± 0.82  | 5.25± 0.89  | 5.02± 0.73  | 35.914**  |
| WBC (×10⁹/L)           | 5.53± 1.16  | 5.71± 1.18  | 5.37± 1.11  | 36.437**  |
| RBC (×10⁹/L)           | 4.60± 0.31  | 4.79± 0.24  | 4.43± 0.28  | 169.042** |
| PDW (fL)               | 17.37± 19.12 | 17.43± 19.54 | 17.31± 18.74 | 0.776**  |
| MPV (fL)               | 10.04± 1.10 | 9.98± 1.09  | 10.09± 1.11 | −12.517*  |
| PLT (×10⁹/L)           | 220.83± 45.74 | 212.11± 43.59 | 228.68± 46.21 | −45.057** |

Table 2. Incidence of metabolic syndrome in different genders. MPV = mean platelet volume. *Metabolic syndrome was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III criteria 3 (NCEP ATP 3). Comparing the incidence of normal and/or Metabolic Syndrome in different genders by Chi-square test. *P < 0.05, **P < 0.01.

| Characteristic   | Incidence (and case number count) in different MPV quartiles | T value |
|-----------------|-------------------------------------------------------------|---------|
|                 | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | Total          |
| Male            |           |           |           |           |                |
| Normal          | 70.01% (5640) | 70.93% (4527) | 70.84% (5189) | 71.80% (4732) | 70.66% (20088) |
| Metabolic syndrome | 29.99% (2416) | 29.07% (1855) | 29.16% (2136) | 29.00% (1933) | 29.34% (8340) |
| Female          |           |           |           |           |                |
| Normal          | 77.21% (6883) | 79.11% (6563) | 80.45% (5363) | 82.01% (6352) | 79.56% (25103) |
| Metabolic syndrome | 22.79% (2032) | 20.89% (1733) | 19.55% (1289) | 17.99% (1393) | 20.44% (6447)  |
| Chi-square value | 113.339** | 130.571** | 172.573** | 244.878** | 637.872**     |
A previous controversial point that MPV was significantly increased in adults with MS. This discrepancy could be due to unhealthy lifestyles in adults like lack of sleep and consumptions of alcohol and many drugs used from adolescence to adulthood. Aypak et al. demonstrated that MPV was inversely related with MS in women, which was in agreement with several previous reports. Park et al. also proved that MPV was negatively correlated with MS, but only in women. He thought PLT counts and MPV were influenced by different factors such as race, smoking habits, gender, physical activity and alcohol consumption. In addition, men tend to have a higher rate of smoking than women. Park et al. argued that in contrast to men with much confounding factors, women, especially pre-pubertal girls were the better group for testifying the association between MS and MPV, and the results should be more reliable.

There are some limitations in our investigations. Firstly, it was a cross-sectional design which cannot confirm the casual relationship. Prospective and interventional studies are essential to explain the causality question in the future. Secondly, although we filtered the subjects according to strict exclusion criteria, some volunteers weren’t aware of their healthy condition, which could have led to error in our investigation. Thirdly, we did not measure inflammatory cytokines such as interleukin and tumor necrosis factor α in this project because of a budget shortage. Similarly, insulin resistance was not measured in this study due to a budget shortage as well. Finally, detailed food recall and some other consumed drugs, which could influence hematological parameters or metabolism, should be recorded in specific details for risk stratification in further research.

### Table 3. Pearson bivariate correlation coefficients. BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, ALT = alanine aminotransferase, Cr = creatinine, TC = total cholesterol, TG = triglycerides, HDL = high-density lipoprotein cholesterol, GLU = glucose, WBC = leukocyte, RBC = erythrocyte, MPV = mean platelet volume, PLT = platelet. *P < 0.05, **P < 0.01.

|       | MPV in male | MPV in female |
|-------|-------------|---------------|
| Age   | −0.057**    | −0.022**      |
| Weight| 0.034**     | −0.010        |
| BMI   | 0.026**     | −0.011        |
| Waist | 0.017**     | −0.014**      |
| SBP   | −0.028**    | −0.043**      |
| DBP   | −0.025**    | −0.034**      |
| ALT   | 0.062**     | 0.016**       |
| Cr    | −0.005**    | −0.019**      |
| TC    | −0.046**    | −0.071**      |
| TG    | 0.022**     | −0.041**      |
| HDL   | 0.006       | 0.017**       |
| GLU   | −0.051**    | −0.085**      |
| WBC   | 0.020**     | −0.010        |
| RBC   | 0.058**     | −0.003        |
| PLT   | −0.388**    | −0.413**      |

### Discussion

The association between MPV and MS has been reported with controversies. In the current study, we demonstrated that MPV was inversely related with MS in women, which was in agreement with several previous reports. Aypak et al. demonstrated that the MPV was positively associated with MS in pre-pubertal girls. He dismissed a previous controversial point that MPV was significantly increased in adults with MS. This discrepancy could be due to unhealthy lifestyles in adults like lack of sleep and consumptions of alcohol and many drugs used from adolescence to adulthood. Aypak et al. argued that it should be worth noting that drugs, such as clopidogrel, statins and angiotensin-converting enzyme inhibitors which could influence MPV levels, were often used in adults with MS. Park et al. also proved that MPV was negatively correlated with MS, but only in women. He thought PLT counts and MPV were influenced by different factors such as race, smoking habits, gender, physical activity and alcohol consumption. In addition, men tend to have a higher rate of smoking than women. Park et al. argued that in contrast to men with much confounding factors, women, especially pre-pubertal girls were the better group for testifying the association between MS and MPV, and the results should be more reliable.

The underlying reason of the relationship among MPV, PLT and MS deserves discussion. It has been suggested that the MPV directly associated with PLT aggregation function. Furthermore, PLT aggregation function has been proven to be increased not only both in acute coronary syndrome and in the presence of cardiovascular risk factors such as DM, hypertension and dyslipidemia. Higher MPV can increase volume of PLTs and enable more active abilities of metabolism and enzymatic reactions. Hence, bigger PLTs have greater prothrombotic factors such as DM, hypertension and dyslipidemia. The relationship between PLT and MS was shown by Zhou et al., who illustrated that PLT count was a protective factor for MS for men, but a risk factor for women. The mechanism linking PLT and MS could be due to unhealthy lifestyles in adults like lack of sleep and consumptions of alcohol and many drugs used from adolescence to adulthood. Aypak et al. argued that in contrast to men with much confounding factors, women, especially pre-pubertal girls were the better group for testifying the association between MS and MPV, and the results should be more reliable.

There are some limitations in our investigations. Firstly, it was a cross-sectional design which cannot confirm the casual relationship. Prospective and interventional studies are essential to explain the causality question in the future. Secondly, although we filtered the subjects according to strict exclusion criteria, some volunteers weren’t aware of their healthy condition, which could have led to error in our investigation. Thirdly, we did not measure inflammatory cytokines such as interleukin and tumor necrosis factor α in this project because of a budget shortage. Similarly, insulin resistance was not measured in this study due to a budget shortage as well. Finally, detailed food recall and some other consumed drugs, which could influence hematological parameters or metabolism, should be recorded in specific details for risk stratification in further research.
Table 4. The risks of MS according to MPV quartiles. MPV = mean platelet volume, OR = odds ratio, CI = confidence interval. *Metabolic Syndrome was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III criteria 3 (NCEP ATP 3). Logistic regression model with quartile 1 as reference, including no covariates. $Logistic regression model with quartile 1 as reference, including age, BMI as covariates. *P < 0.05, **P < 0.01.

In conclusion, this research proves that increased MPV is inversely associated with the risk of developing MS in Chinese women, but not in men. A larger scale and prospective study should be performed in the future for further verification and validation.

Methods

Design. A cross-sectional, community-based health-check program has been commenced in Tianjin Medical University General Hospital since 2007, with assistance of many departments. Written consents were obtained and the protocol was developed and executed as previously by our group18,22–29. Briefly, we asked all of the self-reported healthy participants to fill out a questionnaire. After collecting personal information, blood samples were obtained. In order to avoid influential factors, subjects meeting any of the following criteria were excluded: participants with histories of hepatic, hematological, inflammatory, infectious, renal, cardiovascular, gastro-intestinal, thyroidal, immunological or oncological diseases; participants taking any medicine that might influence WBC, inflammation, tuberculosis; TG higher than 6.0 mmol/L, SBP higher than 180 mmHg, GLU higher than 10.0 mmol/L. A total of 59976 (28428 male, 31548 female) eligible patients were admitted to this research from September 2010 to September 2015.

Informed consent. All participants in this research provided their written consents.

Ethics. The institutional review board and ethic committee of Tianjin Medical University General Hospital approved the ethical, methodological and protocol aspects of this investigation. We confirm that all methods in the current study were carried out in accordance with the relevant guidelines and regulations.

Sample and measurement. When the participants visited our department, anthropometric measurements, as well as fasting blood were tested. Body height (BH) and body weight (BW) were measured without wearing heavy coats and without shoes, and BMI was calculated as weight divided by height squared (kg/m²). Peripheral venous blood samples were collected for indicators: GLU, TC, HDL, ALT, Cr, and TG were determined by an automated analyzer (Hitachi Corporation, Tokyo, Japan); PLT, MPV are measured on an automated hematology analyzer (Sysmex Corporation, Kobe, Japan). We found that sampled platelets swell in an EDTA tube as time increases and consequently MPV values increase. So MPV was analyzed in 1 hour.

Definition. MS was determined according to the National Cholesterol Education Program Adult Treatment Panel III criteria 3. Thus, MS was defined by the presence of three or more of those criteria: (1) Abdominal obesity (waist circumference >88 cm in women, and >102 cm in men); (2) A high TG level ≥1.7 mmol/L; (3) A low HDL cholesterol level <1.3 mmol/L for women, and <1.0 mmol/L for men; (4) A high blood pressure (systolic, ≥130 mm Hg and/or diastolic, ≥85 mm Hg); (5) A high GLU concentration ≥6.1 mmol/L.

Statistical analysis. We used Kolmogorov-Smirnov to assess normality of distribution of continuous variables. All continuous variables were presented as mean ± standard deviation (SD). Differences of the parameters between males or females were evaluated by independent sample’s t test. Then, MPV was divided into quartiles. Prevalence differences were compared by Chi-square test. Pearson bivariate correlation was calculated among MPV and other variables. Binary logistic regression analysis was performed to analyze the odds ratio of MS in different MPV levels, with adjustment. We used automated regression to select variables, which were included in Binary logistic regression. All analyses were conducted using Statistical Product and Service Solutions (SPSS version 17.0, Chicago, IL, USA). Statistical significance was defined as P < 0.05.

References

1. Grundy, S. M. et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Arteriosclerosis, thrombosis, and vascular biology 24, e13–18, https://doi.org/10.1161/01.ATV.0000111245.75752.C6 (2004).
2. National Cholesterol Education Program Expert Panel on Detection, E. & Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106, 3143–3421 (2002).
3. Pal, S. & Ellis, V. The chronic effects of whey proteins on blood pressure, vascular function, and inflammatory markers in overweight individuals. Obesity 18, 1354–1359, https://doi.org/10.1038/oby.2009.397 (2010).

4. Dehghani, M. R., Rezaei, Y., Fakour, S. & Arjmand, N. White Blood Cell Count to Mean Platelet Volume Ratio Is a Prognostic Factor in Patients with Non-ST Elevation Acute Coronary Syndrome with or without Metabolic Syndrome. Korean circulation journal 46, 229–238, https://doi.org/10.4070/kcj.2016.46.2.229 (2016).

5. Nechita, A., et al. Metabolic syndrome and mean platelet volume variation in patients with chest pain and negative cardiac enzymes. Journal of medicine and life 6, 156–160 (2013).

6. Tavil, Y. et al. Mean platelet volume in patients with metabolic syndrome and its relationship with coronary artery disease. Thrombosis research 120, 245–250, https://doi.org/10.1016/j.thromres.2006.10.005 (2007).

7. Dormandy, J. A. et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PRoACT Study (PRospective pioglitAzone Clinical Trial In macrovascular Events): a randomised controlled trial. Lancet 366, 1279–1289, https://doi.org/10.1016/S0140-6736(05)67328-9 (2005).

8. Ayapal, C., Tureli, O., Bircan, M. A. & Yuce, A. Could mean platelet volume among complete blood count parameters be a surrogate marker of metabolic syndrome in pre-pubertal children? Platelets 25, 393–398, https://doi.org/10.1080/09537104.2013.827783 (2014).

9. Lee, E. Y., Kim, S. J., Song, Y. J., Choi, S. J. & Song, I. Immature platelet fraction in diabetes mellitus and metabolic syndrome. Thrombosis research 132, 692–695, https://doi.org/10.1016/j.thromres.2013.09.035 (2013).

10. Demirtunc, R., Duman, D. & Basar, M. Effects of doxazosin and amlopidine on mean platelet volume and serum serotonin level in patients with metabolic syndrome: a randomized, controlled study. Clinical drug investigation 27, 435–441 (2007).

11. Vizzioli, L., Muscari, S. & Muscari, A. The relationship of mean platelet volume with the risk and prognosis of cardiovascular diseases. International journal of clinical practice 63, 1509–1515, https://doi.org/10.1111/j.1742-1241.2009.02070.x (2009).

12. Shah, B., Sha, D., Xie, D., Mohler, E. R. 3rd & Berger, J. S. The relationship between diabetes, metabolic syndrome, and platelet activity as measured by mean platelet volume: the National Health And Nutrition Examination Survey, 1999-2004. Diabetes care 35, 1074–1078, https://doi.org/10.2337/dc11-1724 (2012).

13. Jesri, A., Okonofua, E. C. & Egan, B. M. Platelet and white blood cell counts are elevated in patients with the metabolic syndrome. Journal of clinical hypertension 7, 705–711; quiz 712–703 (2005).

14. Park, B. J. et al. The relationship of platelet count, mean platelet volume with metabolic syndrome according to the criteria of the American Association of Clinical Endocrinologists: a focus on gender differences. Platelets 23, 45–50, https://doi.org/10.3109/09537104.2011.589014 (2012).

15. Coban, E. & Afacan, B. The effect of rosuvastatin treatment on the mean platelet volume in patients with uncontrolled primary dyslipidemia with hypolipidemic diet treatment. Platelets, 111–114 – https://doi.org/10.1080/0953710712034444 (2008).

16. Jagoop, I. A. & Mikhailidis, D. P. Angiotensin II can induce and potentiate shape change in human platelets: effect of losartan. Journal of human hypertension 14, 581–585 (2000).

17. Matsagas, M., Jagoop, I. A., Geroulakos, G. & Mikhailidis, D. P. The effect of a loading dose (300 mg) of clopidogrel on platelet function in patients with peripheral arterial disease. Clinical and applied thrombosis/hemostasis: official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 9, 115–120 (2003).

18. Zhou, P. et al. The associations between leukocyte, erythrocyte or platelet, and metabolic syndrome in different genders of Chinese. Medicine 95, e1589, https://doi.org/10.1097/MD.0000000000001589 (2016).

19. Baoutt, S. Interleukin-6 and megakaryocytopenia: an update. Annals of hematology 73, 157–162 (1996).

20. Jones, R. L., Paradise, C. & Peterson, C. M. Platelet survival in patients with diabetes mellitus. Platelets 25, 393–398, https://doi.org/10.1080/09537104.2013.827783 (2014).

21. Meng, Z. et al. Gender and Age Impact on the Association Between Thyroid-Stimulating Hormone and Serum Lipids. Medicine 94, e2186, https://doi.org/10.1097/MD.0000000000002186 (2015).

22. Meng, Z. et al. Gender and Age Impacts on the Association Between Thyroid Function and Metabolic Syndrome in Chinese. Medicine 94, e2193, https://doi.org/10.1097/MD.0000000000002193 (2015).

23. Liu, L. et al. Relationship between lifestyle choices and hyperuricemia in Chinese men and women. Clinical rheumatology 32, 233–239, https://doi.org/10.1007/s10067-012-2180-z (2013).

24. Ren, X. et al. No associations exist between mean platelet volume or platelet distribution width and thyroid function in Chinese. Medicine 95, e4573, https://doi.org/10.1097/MD.0000000000004573 (2016).

25. Wang, S. et al. Association between liver function and metabolic syndrome in Chinese men and women. Scientific reports 7, 44844, https://doi.org/10.1038/srep44844 (2017).

26. Zhang, J. et al. Gender impact on the correlations between subclinical thyroid dysfunction and hyperuricemia in Chinese. Clinical rheumatology 35, 143–149, https://doi.org/10.1007/s10067-015-2867-4 (2016).

27. Zhang, Q., Lou, S., Meng, Z. & Ren, X. Gender and age impacts on the correlations between hyperuricemia and metabolic syndrome in Chinese. Clinical rheumatology 30, 777–787, https://doi.org/10.1007/s10067-010-1666-7 (2011).

28. Liu, X. et al. Waist Circumference and Subclinical Thyroid Dysfunction in a Large Cohort of Chinese Men and Women. Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, https://doi.org/10.4158/EP-2018-0061 (2018).

Acknowledgements

This study was supported by the National Key Clinical Specialty Project (awarded to the Departments of Nuclear Medicine and Radiology). This study was supported by Tianjin Medical University General Hospital New Century Excellent Talent Program; Young and Middle-aged Innovative Talent Training Program from Tianjin Education Committee; and Talent Fostering Program (the 131 Project) from Tianjin Education Committee, Tianjin Human Resources and Social Security Bureau (awarded to Zhaowei Meng). This study was supported by China National Natural Science Foundation grant 81571709, Key Project of Tianjin Science and Technology Committee Foundation grant 16JCZDJC4300 (awarded to Zhaowei Meng). This study was also supported by Tianjin Science and Technology Committee Foundation grants 11ZCGYSY50700, 12ZCZDSY20400, 13ZCZDSY20200 and (awarded to Qing Zhang, Qiyu Jia and Kun Song). This study was also supported by China National Natural Science Foundation grant #18172235, #18170353 and #18032383, Tianjin Science and Technology Committee Foundation grant #17JCYBJC25400, #15JYFYSY00020 and #15JCYBJC28000. The language and grammar of the manuscript was reviewed and modified by Andrew Murphy, BSEE, JD, Attorney at Law (P.C. 3601N. Classen Blvd. #106, Oklahoma City, OK 73118). This manuscript was reviewed and modified by Kai Jin Associate data scientist, Bold Lab LLC., 1 Hallidie Plaza, San Francisco, CA, 94102). This article was reviewed by Wei Liang, principal statistical consultant and president at WL ClinStat Inc, USA.
Author Contributions
Zhaowei Meng, Ming Liu and Qing Zhang designed the investigation. Fengxiao Zhao, Ziyu Yan, Zhaowei Meng, Xue Li, Xiaojun Ren, Mei Zhu, Qing He, Kun Song, Qiyu Jia, Chunmei Zhang, Huiying Wang, Xiaoxia Liu, Xuemei Zhang, Xiaoran Wang, Zhenghou Pan, Xiangxiang Liu and Wan Zhang conducted the investigation and collected data. Fengxiao Zhao, Ziyu Yan and Zhaowei Meng performed the statistics. Fengxiao Zhao, Ziyu Yan and Zhaowei Meng wrote the main manuscript. All authors reviewed the manuscript.

Additional Information

Competing Interests: The authors declare no competing interests.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.