The relationship between blood lipids and plasma amyloid beta is depend on blood pressure: a population-based cross-sectional study

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Abstract

Background: It is believed that deposition of amyloid beta (Aβ) in the brain is the central pathological changes of Alzheimer’s disease (AD), which triggers a series of pathological processes. However, the relationship between dyslipidemia and AD is uncertain. Considering the peripheral Aβ levels are related to brain Aβ deposition, we explore the relationships between blood lipids and plasma Aβ.

Methods: Participants who lived in the selected village of Xi’an for more than 3 years were enrolled, aged 40–85 years (n = 1282, 37.9% male). Fasting blood lipid, plasma Aβ levels, basic information and living habits were measured. Multiple linear regressions were used.

Results: In total population, blood lipids were not associated with plasma Aβ. After stratified by blood pressure, serum total cholesterol (TC) and low-density lipoprotein (LDL-c) were positively associated with plasma Aβ42 levels (β TC = 0.666, P TC = 0.024; β LDL-c = 0.743, P LDL-c = 0.011, respectively) in normal blood pressure. LDL-c was negatively associated with plasma Aβ40 levels (β = −0.986, P = 0.037) in high blood pressure.

Conclusion: Elevated plasma Aβ42 levels are associated with higher TC and LDL-c in normal blood pressure. Elevated plasma Aβ40 levels are associated with lower LDL-c in high blood pressure. This indicated that the relationships between blood lipids and plasma Aβ were confounded by blood pressure.

Keywords: Alzheimer’s disease, Amyloid beta, Blood lipids, Blood pressure

Introduction

Alzheimer’s disease (AD) is the most common cause of dementia. Toxic plaque formed by the deposition of amyloid beta (Aβ) peptide in the brain is the main characteristic pathogenesis of AD [1]. Aβ peptides are natural products of metabolism consisting of 39 to 43 amino acids, formed by fragmentation of amyloid-β protein precursor (APP) through the sequential enzymatic actions of secretases [2]. In the process of Aβ formation, APP is first cleaved by β-secretase (known as BACE1), releasing sAPPβ into the extra cellular fluid and cerebrospinal fluid (CSF). The remaining fragment is then cleaved by γ-secretase to produce damaging amyloid-β42 (Aβ42) and other Aβ isoform (Aβ40 down to Aβ17). In addition, full-length APP is also cleaved by β and α-secretase to form Aβ16 down to Aβ13 [3]. Under normal circumstance, most of the production is amyloid-β40 (Aβ40) and only a small amount of Aβ42 which is more likely to deposit and has neurotoxic. Aβ present in the brain can be eliminated by various means, including degradation of Aβ degrading enzymes, cell clearance, blood brain barrier (BBB) transport, CSF and interstitial lymphatic drainage, clearance of peripheral cells and tissues, etc. Due to the imbalance of Aβ production and clearance, a large number of neuritic plaques (formed by Aβ deposition) are present in the cerebral...
cortex, hippocampus, and some subcortical nuclei. Aβ deposition in the brain may be the initiating factor in AD process, which is called “amyloid hypothesis” [4]. It has been suggested that Aβ levels in the brain and plasma are in a dynamic balance. Deposition of Aβ in the brain subsequently affects plasma concentration [5]. Peripheral transport of Aβ can reduce its accumulation in the brain, suggesting that the Aβ concentration in plasma is related to the deposition of Aβ in the brain [6].

Dyslipidemia is one of the important risk factor for cardiovascular disease and stroke. Numerous studies showed that blood lipids were also significantly associated with the risk of AD [7–9], but with conflicting results. Several epidemiological, laboratory research and clinical studies supported the hypothesis that higher levels of cholesterol may induce the development of AD [10–13], while others had not confirmed or reversed association with the risk of AD [14–16]. The effects of blood lipids levels on Aβ deposition in the brain were unclear.

Considering that plasma Aβ concentration is related to cerebral Aβ levels and mounting evidence had indicated that blood pressure is related to plasma Aβ levels significantly, we conducted a cross-sectional study to explore the effects of blood pressure on the relationships between blood lipids and plasma Aβ levels in a community population.

Methods
Participants
From October 2014 to March 2015, all aged 40 or more villagers in Qubao village which taken by cluster sampling method near Xi’an were enrolled. There were similar life-styles and population composition between this village and other rural areas of Xi’an. Inclusion criteria: 1) resident villager or who has lived in this area for 3 years or more, 2) agree to participate in this study and provided informed consent (N = 2011). Exclusion criteria: 1) severe cardiac, pulmonary, liver, kidney dysfunction, hematological, acute infection, or tumors, 2) those who have taken lipid-lowering drugs (n = 70), 3) those who showed aberrant plasma Aβ42, Aβ40 levels (n = 529) or blood lipids levels (n = 2) (exceeding 3 standard deviations from the mean), 4) sample hemolysis (n = 128). Total of 1282 participants were included in our analysis (Fig. 1).

Definition of covariates
The diseases and related conditions involved in this study are defined according to the guidelines [17, 18] as follows: 1) A person with a current systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg is defined as high blood pressure. On the contrary, it is defined as normal blood pressure. Blood pressure measured with taking antihypertensive drugs and/or a current SBP ≥140 mmHg and/or a DBP ≥90 mmHg is defined as a hypertensive patient. 2) High fasting blood glucose (FBG) was defined as at least 7 mmol/L. 3) According the guidelines for the prevention and treatment of dyslipidemia in Chinese adults (revised edition 2016), high serum total cholesterol (TC) was defined as at least 5.18 mmol/L, high triglyceride (TG) was defined as at least 1.70 mmol/L, high serum low-density lipoprotein (LDL-c) was defined as at least 3.37 mmol/L and low serum high-density lipoprotein (HDL-c) was defined as less than 1.04 mmol/L. Any abnormality in blood lipids is defined as dyslipidemia. 4) Apolipoprotein E (ApoE ε4) carriers were defined as having at least one allele of ε4, while non-carriers referred to the ones without any ε4 allele.

Questionnaire survey
A uniform questionnaire was used for all subjects, first of all, face to face consultation to collect general information, followed by physical examination and blood sample collection.
Blood pressure measurement
Blood pressure (BP) was measured by a nurse using a mercury sphygmomanometer on each participant’s right arm with a regular adult cuff (Shanghai Medical Instruments Co. Shanghai, China) in the morning, before breakfast (from 8 a.m. to 10 a.m.). Setting BP was measured again after 10 min of rest, and the average of the twice was recorded.

Laboratory evaluation
All subjects were collected 5 ml of venous blood sample from 8 a.m. in the morning (at least 8 h on an empty stomach). 1) Then the blood sample was placed in a serum tube containing a coagulant and was gently inverted upside and down and stood for 30 min. Next, the sample was centrifuged at 3000 rpm for 15 min at room temperature for 2 h and quickly stored at −80 °C until later measurement. TC, TG, HDL-c and LDL-c levels were detected by enzymatic method using an automated biochemical analyzer (C501, Roche, Sweden). Quality indicators accord with the quality requirements set by the US National Cholesterol Education Program. 2) Plasma levels of Aβ40, Aβ42 were measured with commercially available quantitative enzyme-linked immunosorbent assay kits (ELISA, Yuanye Co. Shanghai, China), and the sensitivity of each assay was 1.0 pg/ml, respectively. Measurements were performed using an RT-6000 analyzer (Rayto Co. Shenzhen, China) at 450 nm, and concentrations were calculated from the standard curve. All measurements were performed in duplicate and the results averaged. The intra-assay and inter-assay coefficients of variation were less than 7 and 9%, respectively. 3) Determination of ApoE genotypes: According to manufacturer’s protocol, genomic DNA from blood samples in the EDTA anticoagulant tubes was extracted by blood genomic deoxyribonucleic acid (DNA) extraction kit (Tiangen Co. Beijing, China). We amplified 244 base pair of the ApoE gene fragment using a polymerase chain reaction (PCR) thermocycler, the length of which included two polymorphic sites at amino acid residues 112 and 158(15). Sequence of the PCR products was tested by Sanger

| Characteristics                  | Total (n = 1282) | Dyslipidemia (n = 644) | Normal blood lipids (n = 638) | t or U or Chi square df | P value |
|----------------------------------|------------------|------------------------|-------------------------------|-------------------------|---------|
| Age, years                       | 55.70 (10.19)    | 56.74(10.1)            | 54.66(10.19)                  | −3.673                  | 1280    | <0.001 |
| Male, n(%)                       | 486(37.9)        | 242(37.6)              | 244(38.2)                     | 0.061                   | 1       | 0.806  |
| Education, years                 | 7(4.8)           | 7(3.8)                 | 7(5.9)                        | 190.4615                | −       | 0.023  |
| Hypertension, n(%)               | 601(46.9)        | 356(55.3)              | 245(38.4)                     | 36.663                  | 1       | <0.001 |
| Diabetes mellitus, n(%)          | 146(11.4)        | 91(14.1)               | 55(8.6)                       | 9.641                   | 1       | 0.002  |
| Cardiovascular disease, n(%)     | 73(5.7)          | 40(6.2)                | 33(5.2)                       | 0.644                   | 1       | 0.422  |
| Transient ischemic attack, n(%)  | 23(1.8)          | 13(2.0)                | 10(1.6)                       | 0.370                   | 1       | 0.543  |
| Stroke, n(%)                     | 72(5.6)          | 41(6.4)                | 31(4.9)                       | 1.374                   | 1       | 0.241  |
| Smoking, n(%)                    | 349(27.2)        | 170(26.4)              | 179(28.1)                     | 0.445                   | 1       | 0.505  |
| Drinking, n(%)                   | 168(13.1)        | 93(14.4)               | 76(11.8)                      | 2.030                   | 1       | 0.154  |
| Lack of physical activity, n(%)  | 225(17.6)        | 123(19.1)              | 102(16.0)                     | 2.145                   | 1       | 0.143  |
| Pulse rate, bpm                  | 75.48(8.74)      | 75.51(8.58)            | 75.44(8.90)                   | −0.151                  | 1280    | 0.880  |
| Waistline, cm                    | 84.76(8.96)      | 86.82(8.99)            | 82.68(8.44)                   | −8.482                  | 1280    | <0.001 |
| Hip circumference, cm            | 96.39(6.56)      | 97.48(6.76)            | 95.28(6.17)                   | −6.091                  | 1280    | <0.001 |
| BMI, kg/m²                       | 25.13(3.20)      | 25.69(3.32)            | 24.57(2.98)                   | −6.346                  | 1297.91 | <0.001 |
| SBP, mmHg                        | 132.16(19.08)    | 135.62(19.58)          | 128.67(17.92)                 | −6.637                  | 1272.03 | <0.001 |
| DBP, mmHg                        | 81.82(10.44)     | 83.63(10.83)           | 80.00(9.72)                   | −6.315                  | 1267.75 | <0.001 |
| FBG, mmol/L                      | 5.39(5.06, 5.77) | 5.42(5.07, 5.91)       | 5.35(5.06, 5.69)              | 188.237                 | −       | 0.009  |
| TG, mmol/L                       | 1.43(1.03,1.99)  | 1.99(1.48, 2.47)       | 1.100(1.88, 1.39)             | 53.420                  | −       | <0.001 |
| TC, mmol/L                       | 5.04(1.01)       | 5.57(1.02)             | 4.510(0.64)                   | −22.296                 | 1086.03 | <0.001 |
| LDL-c, mmol/L                    | 3.31(0.89)       | 3.78(0.89)             | 2.839(0.56)                   | −22.888                 | 1085.95 | <0.001 |
| HDL-c, mmol/L                    | 1.41(0.31)       | 1.37(0.32)             | 1.46(0.30)                    | 5.168                   | 1280    | <0.001 |
| ApoE ε4, n(%)                    | 173(13.5)        | 92(14.3)               | 81(12.7)                      | 0.180                   | 2       | 0.667  |

Unpaired Student’s t-test and mean ± SD were used to compare the difference of the approximately normally distributed continuous variables between dyslipidemia and normal blood lipids. Mann-Whitney U test and median (quartile) were used for the skew distributional data and Chi square and percentage were used for categorical variables. Data are mean (SD), median (interquartile range), or number (percentage). BMI, body mass index. SBP, systolic blood pressure. DBP, diastolic blood pressure. FBG, fast blood glucose. TC, total cholesterol. TG, triglyceride. HDL-c, high-density lipoprotein. LDL-c, low-density lipoprotein. ApoE, apolipoprotein E.
Correlations of TC, Log TG, HDL-c, LDL-c and plasma Aβ42 in total study population. Simple linear correlations between TC, Log TG, HDL-c, LDL-c and plasma Aβ42 were shown respectively in picture (a, b, c, d).

Table 2: Comparison of plasma Aβ in Dyslipidemia group and Normal blood lipids in total study population (n = 1282)

|                     | Aβ42 (pg/ml) | Aβ40 (pg/ml) |
|---------------------|--------------|--------------|
|                     | mean (SD)    | t            | df       | P     | mean (SD)    | t            | df       | P     |
| Dyslipidemia (n = 644) | 40.97(6.11)  | −0.889       | 1269.67  | 0.374 | 52.31(8.79)  | 0.865       | 1280     | 0.387 |
| Normal blood lipids (n = 638) | 40.65(6.62)  | 52.74(9.04)  |           |       |             |             |          |       |
| High TC (n = 515)    | 41.11(6.16)  | −1.389       | 1142.34  | 0.165 | 52.20(8.96)  | 1.077       | 1280     | 0.282 |
| Normal TC (n = 767)  | 40.61(6.50)  |             |          |       | 52.74(8.89)  |             |          |       |
| High TG (n = 447)    | 40.98(6.03)  | −0.715       | 1280     | 0.475 | 52.65(8.91)  | −0.371      | 1280     | 0.710 |
| Normal TG (n = 835)  | 40.72(6.54)  |             |          |       | 52.46(8.92)  |             |          |       |
| High LDL-c (n = 544) | 41.10(6.03)  | −1.398       | 122,239  | 0.162 | 52.09(8.96)  | 1.485       | 1280     | 0.138 |
| Normal LDL-c (n = 738) | 40.60(6.60)  |             |          |       | 52.84(8.88)  |             |          |       |
| Low HDL-c (n = 116)  | 40.89(6.48)  | −0.142       | 1280     | 0.887 | 53.18(9.34)  | −0.825      | 1280     | 0.409 |
| Normal HDL-c (n = 1166) | 40.80(6.36)  |             |          |       | 52.46(8.87)  |             |          |       |

Unpaired Student’s t–test were used to compare the difference of plasma Aβ42, Aβ40 between the groups of the covariates. Data are shown as mean (SD). Aβ, amyloid beta. TC, total cholesterol. TG, triglyceride. HDL-c, high-density lipoprotein. LDL-c, low-density lipoprotein.

Fig. 2 Correlations of TC, Log TG, HDL-c, LDL-c and plasma Aβ42 in total study population. Simple linear correlations between TC, Log TG, HDL-c, LDL-c and plasma Aβ42 were shown respectively in picture (a, b, c, d). Aβ, amyloid beta. TC, total cholesterol. TG, triglyceride. HDL-c, high-density lipoprotein. LDL-c, low-density lipoprotein.
sequencing (Sangon Co. Shanghai, China). Finally, we used direct interpretation of the sequencing chromatogram to determine the ApoE genotype.

**Statistical analysis**

Before doing statistical analysis, we tested the distribution of each covariate by using Skewness, Kurtosis and P-P plots. Covariates that nearly conformed to normal distribution included age, pulse rate, waistline, hip circumference, BMI, SBP, DBP, TC, HDL-c, LDL-c which were expressed as mean (SD) and were compared between different groups by using an unpaired Student’s *t*-test. Non-normal distribution covariates included education, levels of TG and FBG were expressed as median (interquartile range) and were compared by Mann-Whitney U-test. Categorical variables were expressed as the number (percentage) and were compared by χ² test. For serum lipid, participants were divided into dyslipidemia group and normal blood lipids group. Differences between two groups were compared. We used simple linear correlation scatter plot to roughly observe the linear trend between blood lipids and plasma Aβ levels. We performed multiple liner regression models to explore the statistical significance of the association after adjusting for other confounding factors including age, sex, education years, smoking, drinking, physical activity level, and history of heart disease, waist circumference, hip circumference, BMI, pulse rate, SBP, DBP, FBG and ApoE ε4 genotype (ApoE is involved in the regulation of Aβ metabolism, aggregation and deposition [19]).

Two secondary analyses were performed. First, associations between blood lipids and Aβ were analyzed in total study population. Because TC was collinear with LDL-c, two models were built. Model 1: TG, TC, HDL-c and other covariates mentioned above. Model 2: TG, LDL-c, HDL-c and other covariates mentioned above. Second, to rule out the possibility of BP affecting the relationship between blood lipids and plasma Aβ, we divided the total population into high blood pressure and normal blood pressure.

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**Fig. 3** Correlations of TC, Log TG, HDL-c, LDL-c and plasma Aβ in total study population. Simple linear correlations between TC, Log TG, HDL-c, LDL-c and plasma Aβ were shown respectively in picture (a, b, c, d). Aβ, amyloid beta. TC, total cholesterol. TG, triglyceride. HDL-c, high-density lipoprotein. LDL-c, low-density lipoprotein.
results

characteristics of the population

As shown in the Table 1, participants with dyslipidemia (n = 644) were older, higher ratios of hypertension, diabetes mellitus, higher levels of BMI, SBP, DBP, FBG, TC, LDL-c, TG and lower levels of education and HDL-c than those with normal lipids.

association between plasma Aβ levels and blood lipids in the total population

In the total population, plasma Aβ levels had no differences between dyslipidemia group and normal lipids group (Table 2). No linear trends were found (Figs. 2, 3). After adjusting for confounding factors as described above, no correlations were found between blood lipids and plasma Aβ levels (Table 3).

Table 3 Multiple linear regression of blood lipids and plasma Aβ levels in total study participants (n = 1282)

|        | Aβ40 (pg/ml) | Aβ42 (pg/ml) |
|--------|--------------|--------------|
|        | β | t | P value | β | t | P value |
| Model 1 | TG | −0.030 | −0.122 | 0.903 | 0.087 | 0.256 | 0.798 |
| | TC | 0.254 | 1.156 | 0.248 | −0.356 | −1.156 | 0.248 |
| | HDL-c | −0.448 | −0.615 | 0.539 | −0.625 | −0.611 | 0.541 |
| | ApoE e4 | 0.955 | 1.813 | 0.070 | 0.278 | 0.376 | 0.707 |
| Model 2 | TG | −0.001 | −0.004 | 0.997 | 0.042 | 0.134 | 0.893 |
| | LDL-c | 0.325 | 1.483 | 0.138 | −0.442 | −1.439 | 0.150 |
| | HDL-c | −0.252 | −0.385 | 0.700 | −0.908 | −0.988 | 0.323 |
| | ApoE e4 | 0.946 | 1.797 | 0.073 | 0.288 | 0.390 | 0.697 |

β, the unstandardized regression coefficient

model 1: adjust for sex, age, education years, smoking, drinking, lack of physical activity, cardiovascular disease, waistline and lip circumference, pulse rate, SBP, DBP, FBG, TC, TG, HDL-c, BMI and ApoE genotype. BMI, body mass index. SBP, systolic blood pressure. DBP, diastolic blood pressure. FBG, fast blood glucose Aβ, amyloid beta. TC, total cholesterol. TG, triglyceride. HDL-c, high-density lipoprotein. LDL-c, low-density lipoprotein. ApoE, apolipoprotein E.

model 2: adjust for sex, age, education years, smoking, drinking, lack of physical activity, cardiovascular disease, waist and lip circumference, pulse rate, SBP, DBP, FBG, LDL-c, TC, HDL-c, BMI and ApoE genotype. BMI, body mass index. SBP, systolic blood pressure. DBP, diastolic blood pressure. FBG, fast blood glucose Aβ, amyloid beta. TC, total cholesterol. TG, triglyceride. HDL-c, high-density lipoprotein. LDL-c, low-density lipoprotein. ApoE, apolipoprotein E.

Association of plasma Aβ levels and blood lipids stratified by blood pressure

In normal blood pressure group, Aβ42 levels were higher in the high TC and high LDL-c group than that in the normal group (Table 5). Positive linear trends were found between TC, LDL-c levels and plasma Aβ42 levels in normal blood pressure group (Fig. 4a, b). Negative linear trend was found between LDL-c levels and plasma Aβ40 levels in high blood pressure group (r = −0.089, P = 0.038). Consistent with previous analysis, TC and LDL-c were independently and positively associated with plasma Aβ42 levels after re-stratified in the normal blood pressure. LDL-c was negatively associated with plasma Aβ40 levels in high blood pressure group (Table 6).

discussion

In this population-based study, we found that TC and LDL-c were positively correlated with plasma Aβ42 levels in normal blood pressure. LDL-c was negatively associated with plasma Aβ40 levels in the high blood pressure. This finding was independent of age, sex, ApoE e4 and other confounding factors. This indicated that the relationships between blood lipids and plasma Aβ were confounded by blood pressure.

Studies have shown that hyperlipidemia may play a role in the development of AD [20]. A 13-year follow-up study showed that higher LDL-c and TC levels were associated with an increased risk of AD [7]. A study containing 7053 community-dwelling elderly suggested low TG was associated with decreased incident AD in women [21]. Elevated HDL-c levels might be associated with a decreased risk of AD were also found in elderly individuals [8]. Therefore, elevated blood lipids may play a role in the progression of AD [9].

However, the relationship between blood lipids and plasma Aβ is not fully determined. Positively correlation of HDL-c levels with Aβ42 in not using statins was observed and no relationships of Aβ42 with TC and LDL-c [22]. Inverse trend was observed between HDL-c and Aβ42 levels, although not significant [23]. Regression analysis considering the multiple influences of baseline parameters TC, LDL-c, HDL-c, TG, BMI, lnHbA1c and presence of at least one ApoE e4 allele on the lnAβ42 at 5 years revealed TC as the only significant predictor. Excluding TC from the list of independent variables, LDL-
c was the single negative predictor [24]. A double-blind, randomized, placebo-controlled study showed that after giving subjects with lovastatin 40 mg or 60 mg per day for 3 months, serum $A_\beta$ concentrations were lower than baseline measurements compared with the placebo group [25]. There was also reports in the literature that pravastatin at 10 mg/d does not decrease plasma levels of either $A_\beta_{40}$ or $A_\beta_{42}$ in humans [26]. The possible reason for the difference between the reported results in the literature and our study may be the research population, inclusion criteria, exclusion criteria and method for measuring $A_\beta$ has not been unified [27]. Compared with the INNO-BIA assay, the ELISA measured $A_\beta_{40}$ levels are slightly lower and $A_\beta_{42}$ levels are slightly higher [27]. Our previous research has proved the methods are credible [28, 29]. More research is still needed.

In present study, we did not find the relationship between dyslipidemia and plasma $A_\beta$ levels in the total population. However, after stratified by blood pressure, we found that TC and LDL-c were positively correlated with plasma $A_\beta_{42}$ levels in normal blood pressure, but not in the hypertension group, indicated that the relationship between blood lipids and $A_\beta$ is confounded by the blood pressure. Hypertension is the most important risk factor for cardiovascular disease and stroke. Also, growing evidence indicate that hypertension is a major risk factor for AD. Hypertension has an effect on blood lipids and $A_\beta$ [30]. Elevated blood pressure had effects on the $A_\beta$ [31–33]. Our previous study found that elevation in PP was associated with increased plasma $A_\beta_{40}$ and decreased log-transformed soluble advanced glycosylation end product-specific receptor (sRAGE), the underlying mechanism may be relevant to peripheral $A_\beta$ clearance [31]. Therefore, we explored the effect of blood pressure on the relationship between blood lipids and plasma $A_\beta$.

The mechanism of dislipidemia related to plasma $A_\beta$ levels is not clear. Hypercholesterolemia may cause the deposition of $A_\beta$ in the brain by affecting the translocation

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### Table 4 Comparisons of High blood pressure group and Normal blood pressure group

| Characteristics     | High blood pressure group ($n = 548$) | Normal blood pressure group ($n = 734$) | t or U or Chi square | df | $P$ value |
|---------------------|--------------------------------------|----------------------------------------|----------------------|----|-----------|
| Age, years          | 59.03 (9.88)                         | 53.21 (9.70)                           | −10.536              | 1280 | <0.001    |
| Male, n(%)          | 210 (38.3)                           | 276 (37.6)                             | 0.069                | 1   | 0.793     |
| Education, years    | 6 (3.8)                              | 8 (5.9)                                | 171,805              | –   | <0.001    |
| Diabetes mellitus, n(%) | 88 (16.1)                        | 58 (7.9)                               | 20.684               | 1   | <0.001    |
| Cardiovascular disease, n(%) | 40 (7.3)                        | 33 (4.5)                               | 4.592                | 1   | 0.032     |
| Transient ischemic attack, n(%) | 12 (2.2)                        | 11 (1.5)                               | 0.851                | 1   | 0.356     |
| Stroke, n(%)        | 46 (8.4)                             | 26 (3.5)                               | 13.934               | 1   | <0.001    |
| Smoking, n(%)       | 145 (26.5)                           | 204 (27.8)                             | 0.281                | 1   | 0.596     |
| Drinking, n(%)      | 74 (13.5)                            | 94 (12.8)                              | 0.134                | 1   | 0.714     |
| Lack of physical activity, n(%) | 112 (20.4)                       | 113 (15.4)                             | 5.514                | 1   | 0.019     |
| Pulse rate, bpm     | 76.35 (9.11)                         | 74.82 (8.40)                           | −3.115               | 1280 | 0.002     |
| Waistline, cm       | 86.77 (9.21)                         | 83.26 (8.47)                           | −6.979               | 1121.85 | <0.001 |
| Hip circumference, cm | 97.41 (6.82)                      | 95.62 (6.25)                           | −4.867               | 1280 | <0.001    |
| BMI, kg/m²           | 25.87 (3.37)                         | 24.58 (2.95)                           | −7.177               | 1087.29 | <0.001 |
| SBP, mmHg           | 149.26 (14.88)                       | 119.39 (9.45)                          | −41.205              | 867.62 | <0.001 |
| DBP, mmHg           | 89.80 (9.65)                         | 75.87 (6.17)                           | −29.572              | 871.13 | <0.001    |
| FBG, mmol/L         | 5.48 (5.15,6.01)                     | 5.32 (5.01,5.66)                       | 163,777              | –   | <0.001    |
| TG, mmol/L          | 1.64 (1.17,2.22)                     | 1.28 (0.97,1.78)                       | 150,027              | –   | <0.001    |
| TC, mmol/L          | 5.14 (1.00)                          | 4.96 (1.00)                            | −3.177               | 1280 | 0.002     |
| LDL-c, mmol/L       | 3.40 (0.88)                          | 3.24 (0.88)                            | −3.182               | 1280 | <0.001    |
| HDL-c, mmol/L       | 1.39 (0.31)                          | 1.43 (0.32)                            | 1.893                | 1280 | 0.059     |
| ApoE ε4, n(%)       | 70 (14.06)                           | 103 (15.42)                            | 0.426                | 2   | 0.808     |
| $A_\beta_{42}$, pg/mL | 40.64 (6.32)                        | 40.94 (6.41)                           | 0.842                | 1280 | 0.400     |
| $A_\beta_{40}$, pg/mL | 53.05 (8.82)                        | 52.13 (8.98)                           | −1.828               | 1280 | 0.068     |

Unpaired Student’s t-test and mean ± SD were used to compare the difference of the approximately normally distributed continuous variables between high blood pressure and normal blood pressure group. Mann-Whitney U test and median (quartile) were used for the skew distributional data and Chi square and percentage were used for categorical variables. Data are mean (SD), median (interquartile range), or number (percentage). BMI, body mass index. SBP, systolic blood pressure. DBP, diastolic blood pressure. FBG, fast blood glucose. $A_\beta$, amyloid beta. TC, total cholesterol. TG, triglyceride. HDL-c, high-density lipoprotein. LDL-c, low-density lipoprotein. ApoE, apolipoprotein E.
|                                | High blood pressure group (n = 548)                  | Normal blood pressure group (n = 734)                  |
|--------------------------------|-----------------------------------------------------|-------------------------------------------------------|
|                                | Aβ42 (pg/ml)                                       | Aβ42 (pg/ml)                                         |
|                                | mean (SD)                                          | mean (SD)                                            | Aβ40 (pg/ml)                                        | mean (SD)                                          | Aβ40 (pg/ml)                                        |
|                                | t                                                  | df                                                   | P                                                  | t                                                  | df                                                   | P                                                  |
| Dyslipidemia (n = 644)         | 40.62(6.09)                                        | 0.095                                                | 546                                                | 0.964                                              | 53.02(8.82)                                         | 0.107                                               | 546                                                | 0.458                                              | 41.32(6.11)                                        | 1.432                                               | 713.43                                              | 0.145                                              | 51.61(8.72)                                        | 1.403                                               | 732                                                | 0.042                                              |
| Normal blood lipids (n = 638)  | 40.67(6.63)                                        |                                                      | 53.10(8.83)                                        | 40.64(6.62)                                        | 0.107                                               | 546                                                | 0.585                                              | 546                                                | 52.54(9.16)                                        | 0.458                                              | 732                                                | 0.043                                              | 51.64(8.92)                                        | 1.120                                               | 732                                                | 0.263                                              |
| High TC (n = 515)              | 40.60(6.01)                                        | 0.113                                                | 52.81(8.98)                                        | 0.385                                              | 546                                                | 0.599                                              | 546                                                | 0.559                                              | 41.57(6.26)                                        | 2.028                                               | 732                                                | 0.043                                              | 51.64(8.92)                                        | 1.120                                               | 732                                                | 0.263                                              |
| Normal TC (n = 767)            | 40.67(6.96)                                        |                                                      | 53.25(8.69)                                        | 40.58(6.47)                                        | 0.107                                               | 546                                                | 0.585                                              | 546                                                | 52.41(9.00)                                        | 0.458                                              | 732                                                | 0.043                                              | 51.64(8.92)                                        | 1.120                                               | 732                                                | 0.263                                              |
| High TG (n = 447)              | 40.85(5.93)                                        | −0.708                                               | 546                                                | 0.479                                              | 53.24(8.88)                                        | −0.469                                              | 546                                                | 0.640                                              | 41.16(6.17)                                        | −0.560                                              | 732                                                | 0.576                                              | 51.90(8.92)                                        | 0.416                                               | 732                                                | 0.677                                              |
| Normal TG (n = 835)            | 40.46(6.62)                                        |                                                      | 52.89(8.78)                                        | 40.86(6.50)                                        | 0.107                                               | 546                                                | 0.585                                              | 546                                                | 52.21(9.00)                                        | 0.458                                              | 732                                                | 0.043                                              | 51.64(8.92)                                        | 1.120                                               | 732                                                | 0.263                                              |
| High LDL-c (n = 544)           | 40.53(5.99)                                        | 0.377                                                | 544.65                                             | 0.706                                              | 52.55(9.09)                                        | 1.240                                               | 546                                                | 0.215                                              | 41.59(6.04)                                        | −2.281                                              | 655.74                                              | 0.023                                              | 51.70(8.84)                                        | 1.063                                               | 732                                                | 0.288                                              |
| Normal LDL-c (n = 738)         | 40.73(6.60)                                        |                                                      | 53.48(8.57)                                        | 40.51(6.61)                                        | 0.107                                               | 546                                                | 0.585                                              | 546                                                | 52.42(9.06)                                        | 0.458                                              | 732                                                | 0.043                                              | 51.64(8.92)                                        | 1.120                                               | 732                                                | 0.263                                              |
| Low HDL-c (n = 116)            | 42.00(6.86)                                        | −1.663                                               | 546                                                | 0.097                                              | 53.54(8.09)                                        | −0.429                                              | 546                                                | 0.668                                              | 39.95(6.04)                                        | 1.281                                               | 732                                                | 0.201                                              | 52.87(10.34)                                       | −0.596                                              | 7078                                                | 0.553                                              |
| Normal HDL-c (n = 1166)        | 40.49(6.25)                                        |                                                      | 53.00(8.90)                                        | 40.13(6.44)                                        | 0.107                                               | 546                                                | 0.585                                              | 546                                                | 52.06(8.84)                                        | 0.458                                              | 732                                                | 0.043                                              | 51.64(8.92)                                        | 1.120                                               | 732                                                | 0.263                                              |

Unpaired Student’s t-test were used to compare the difference of plasma Aβ42, Aβ40 between the groups of the covariates. Data are shown as mean (SD) Aβ, amyloid beta. TC, total cholesterol. TG, triglyceride. HDL-c, high-density lipoprotein. LDL-c, low-density lipoprotein.
of endothelial cells across the BBB [34]. The injured BBB in turn induces inflammation, resulting in an increase gap of brain microvascular endothelial cells [35, 36]. The damage of BBB may affect the expression of low-density lipoprotein receptor-related protein 1 (LRP1) and decrease the function of Aβ transport out of the brain. It may also promotes the expression of RAGE and increase the transport of plasma Aβ to the central nervous system, which ultimately causes Aβ deposition in the brain [37]. These findings suggest that dyslipidemia is associated with increased Aβ deposition in the brain. The process of brain Aβ from the center to the periphery is its main pathway of clearance, elevated plasma Aβ levels associated with increased Aβ deposition in the brain [38]. Therefore, blood lipids are associated with plasma Aβ may relate to the increased deposition of Aβ in the brain.

Recent years, study had also suggested that hyperlipidemia can affect Aβ metabolism [39]. TC is mainly concentrated in membrane microdomains termed lipid rafts where considerable evidence indicates that the amyloidogenic processing of APP largely occurs [39]. TC can enhance the activity of BACE1 (the rate-limiting enzyme for Aβ generation) and promote its localization to lipid rafts, otherwise, it can also act as a positive regulator of γ-secretase to further increase the activity of it [40]. BACE1 transcription increased in mice feed with high-

![Fig. 4 Correlations of TC, LDL-c and plasma Aβ42 in normal blood pressure group. Simple linear correlations between TC, LDL-c and plasma Aβ42 were shown respectively in picture (a, b). Aβ, amyloid beta. TC, total cholesterol. LDL-c, low-density lipoprotein.](image)

### Table 6: Multiple linear regression models of blood lipids and plasma Aβ levels stratified by blood pressure

| Model 3 | High blood pressure group (n = 548) | | | | Normal blood pressure group (n = 734) | | | |
|---|---|---|---|---|---|---|---|---|
| | Aβ42(pg/ml) | Aβ40(pg/ml) | | | Aβ42(pg/ml) | Aβ40(pg/ml) | | |
| | β | t | P | β | t | P | β | t | P |
| TG | 0.661 | 1.849 | 0.065 | 0.618 | 1.220 | 0.223 | −0.532 | −1.609 | 0.108 | −0.224 | −0.480 | 0.631 |
| TC | −0.442 | −1.273 | 0.203 | −0.885 | −1.886 | 0.060 | 0.666 | 2.267 | 0.024 | 0.084 | 0.204 | 0.838 |
| HDL-c | −1.525 | −1.392 | 0.165 | 0.503 | 0.324 | 0.746 | 0.100 | 0.102 | 0.919 | −1.566 | −1.130 | 0.259 |
| ApoE e4 | 0.305 | 0.372 | 0.710 | −0.727 | −0.627 | 0.531 | 1.207 | 1.755 | 0.080 | 1.083 | 1.117 | 0.264 |

| Model 4 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| TG | 0.552 | 1.685 | 0.093 | 0.466 | 1.006 | 0.315 | −0.423 | −1.371 | 0.171 | −0.185 | −0.426 | 0.670 |
| LDL-c | −0.363 | −1.088 | 0.277 | −0.986 | −2.090 | 0.037 | 0.743 | 2.558 | 0.011 | 0.013 | 0.031 | 0.976 |
| HDL-c | −1.942 | −1.935 | 0.053 | −0.259 | −0.182 | 0.855 | 0.689 | 0.786 | 0.432 | −1.435 | −1.160 | 0.247 |
| ApoE e4 | 0.304 | 0.370 | 0.711 | −0.707 | −0.610 | 0.542 | 1.203 | 1.751 | 0.080 | 1.093 | 1.128 | 0.260 |

β, the unstandardized regression coefficient

Model 3: adjust for sex, age, education years, smoking, drinking, lack of physical activity, cardiovascular disease, waistline and lip circumference, pulse rate, SBP, DBP, FGB, TG, HDL-c, BMI and ApoE genotype. BMI, body mass index. SBP, systolic blood pressure. DBP, diastolic blood pressure. FGB, fasting blood glucose Aβ, amyloid beta. TC, total cholesterol. TG, triglyceride. HDL-c, high-density lipoprotein. LDL-c, low-density lipoprotein. ApoE, apolipoprotein E

Model 4: adjust for sex, age, education years, smoking, drinking, lack of physical activity, cardiovascular disease, waist and lip circumference, pulse rate, SBP, DBP, FGB, LDL-c, TG, HDL-c, BMI and ApoE genotype. BMI, body mass index. SBP, systolic blood pressure. DBP, diastolic blood pressure. FGB, fasting blood glucose Aβ, amyloid beta. TC, total cholesterol. TG, triglyceride. HDL-c, high-density lipoprotein. LDL-c, low-density lipoprotein. ApoE, apolipoprotein E
fat and TC, suggesting that hypercholesterolemia increases the production of Aβ by affecting the activity of secretase [41]. In addition, increased TC in cell membranes can inhibit the function of α-secretase, promote the cleavage of APP by β-secretase and γ-secretase, and eventually lead to increased Aβ production [42].

An important question is why TC and LDL-c are related to plasma Aβ_{42} in normal blood pressure, and why LDL-c is correlated with plasma Aβ_{40} in high blood pressure rather than Aβ_{42}. Aβ peptides are mainly produced in the brain, are transported to the cerebrospinal fluid and plasma, and are degraded in the periphery [43]. This degradation is of importance as it allows lowering the whole brain Aβ content. Aβ peptides, particularly Aβ_{42}, are highly water insoluble molecules requiring lipid environments to be transported to the places of their degradation or excretion [44]. In addition, in normal blood pressure, the blood vessels walls are not damaged and transportation of Aβ is unrestricted. This is not the case in high blood pressure, where blood vessels might be damaged and transportation of Aβ peptides is consequently deteriorated. Therefore, in normal blood pressure, Aβ_{42} correlated with TC and LDL-c may as it’s strongly hydrophobic and the integrity of the vascular wall. In high blood pressure, Aβ_{40} peptides negatively associated with LDL-c as lower amount of Aβ peptides are transported through the blood vessels at all. Moreover, Aβ is highly hydrophobic and requires lipid environment for its solubility. Positive correlation of TC and LDL-c with Aβ_{42} might simply reflect the better condition for solubility.

Limitations
First, the design of this study did not allow for causal assumptions between plasma Aβ levels and dyslipidemia. It was difficult to determine whether dyslipidemia led to plasma Aβ change. The results need to be validated in additional longitudinal cohort studies. Second, we did not analyze the relationships of dyslipidemia and plasma Aβ levels in mild cognitive impairment (MCI) or dementia patients because of the rather small sample size. Third, Aβ deposition in the brain or CSF could not be obtained. The effects of peripheral Aβ clearance on brain Aβ accumulation must be investigated. Finally, we did not detect blood oxidized low-density lipoprotein (ox-LDL) level. It has been reported that ox-LDL is more toxic and plays a more important role in the pathogenesis of AD [45].

Conclusions
In summary, our research find that elevated plasma Aβ_{42} levels are associated with higher TC and higher LDL-c in normal blood pressure. Elevated plasma Aβ_{40} levels are associated with lower LDL-c in high blood pressure. This indicated that the relationship between blood lipids and plasma Aβ was confounded by blood pressure. Considering the close relationship between plasma Aβ and deposition in the brain, we explore the relationship between plasma Aβ and blood lipids to provide some help for the auxiliary diagnosis of AD. Additional large-scale cohort studies and convincing evidence-based medical researches are required.

Abbreviations
AD: Alzheimer’s disease; APP: Amyloid beta protein precursor; Aβ: Amyloid beta; BBB: Blood brain barrier; DBP: Diastolic blood pressure; FBG: Fast blood glucose; HDL-c: High-density lipoprotein; LDL-c: Low-density lipoprotein; LRP1: Low-density lipoprotein receptor-related protein 1; PCR: Polymerase chain reaction; PP: Pulse pressure; RAGE: Advanced glycosylation end product-specific receptor; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Triglyceride

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Authors’ contributions
HNW took part in the survey, did the statistical analysis and wrote the manuscript. GL performed the analysis and data acquisition. SSH designed the study, collected and took part in the statistical analysis. WS contributed to the treatment of the blood specimens. CC, JY, DLJ, WJ, HK, DMY, and WYJ took part in the survey and collected samples. QQM provided technical guidance in all stages of the study. All authors have read and approved the final article.

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Availability of data and materials
The data used in this study are available from the corresponding author if needed.

Ethics approval and consent to participate
All individuals received information about the study and were able to cooperate to complete the questionnaire survey. For illiterate participants, their relatives agreed on the informed consent. The privacy rights of the participants had always been observed. The Ethics Committee of The First Affiliated Hospital of Xi’an Jiaotong University gave ethical approval.

Consent for publication
All the participants provided written informed consent for the publication of the results of this study.

Competing interests
The authors declare that they have no competing interests.

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