Association between MTHFR C677T polymorphism and abdominal aortic aneurysm risk
A comprehensive meta-analysis with 10,123 participants involved

Jie Liu, MDa, Xin Jia, MDb, Haifeng Li, MDb, Senhao Jia, MDa, Minhong Zhang, MD, PhDa, Yongle Xu, MD, PhDa, Xin Du, MDa, Nianrong Zhang, MD, PhDc, Weihang Lu, MDb, Wei Guo, MDa,*

Abstract
Background: Abdominal aortic aneurysm (AAA) is a life-threatening condition. A number of studies reported the association between methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and AAA risk, but substantial controversial findings were observed and the strength of the association remains unclear.

Objective: The aim of this study was to investigate the aforementioned association in the overall population and different subgroups.

Methods: PUBMED and EMBASE databases were searched until March 2016 to identify eligible studies, restricted to humans and articles published in English. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the susceptibility to AAA. Subgroup meta-analyses were conducted on features of the population, such as ethnicity, sex of the participants, and study design (source of control).

Results: Twelve case–control studies on MTHFR C677T polymorphism and AAA risk, including 3555 cases and 6688 case-free controls were identified. The results revealed no significant association between the MTHFR C677T polymorphism and AAA risk in the overall population and within Caucasian or Asian subpopulations in all 5 genetic models. Further subgroup meta-analysis indicated that significantly increased risks were observed among cases with a mean age <70 years (OR=1.73, 95% CI=1.10–2.12, P=0.02), cases with prevalence of smoking <60% (OR=1.39, 95% CI=1.02–1.90, P=0.04), and cases with aneurysm diameter ≥55mm (OR=1.55, 95% CI=1.07–2.24, P=0.02) in the dominant genetic model. No publication bias was detected in the present study.

Conclusion: In conclusion, our comprehensive meta-analysis suggests that the MTHFR C677T polymorphism may play an important role in AAA susceptibility, especially in younger, non-smoking, larger AAA-diameter subgroups of patients.

Abbreviations: AAA=abdominal aortic aneurysm, CI=confidence interval, Hcy=homocysteine, MTHFR=methylenetetrahydrofolate reductase, OR=odds ratio.

Keywords: abdominal aortic aneurysm, homocysteine, metaanalysis, methylenetetrahydrofolate reductase

1. Introduction
Abdominal aortic aneurysm (AAA) is a life-threatening condition detected in up to 9% of men ages >65 years in Western populations.[1–4] Several risk factors are recognized, such as age >65 years, maleness, smoking, and a positive family history of AAs. Protective factors include type-2 diabetes mellitus, African-American ethnicity, and femaleness.[5,6] Although many risk factors have been identified, the etiology of AAA is still largely unclear.[7,8]

Homocysteine (Hcy) is a sulfur-containing nonessential amino acid that functions as a key intermediate in the methionine metabolism. Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme involved in Hcy metabolism. A common functional polymorphism (C677T) in the gene-encoding MTHFR results in a 70% reduction in enzymatic activity, in vitro, and has been associated with differences in Hcy concentration.[9,10] Previous studies on the MTHFR C677T polymorphism suggested a causal link between hyperhomocysteinemia (HHcy), characterized by elevated Hcy levels in the blood, coronary heart disease, stroke, and peripheral vascular disease.[11,12]

However, studies investigating the association between HHcy and AAA yielded conflicting results.[13–20] Whether Hcy levels play a causal role in the pathogenic process of AAA remains unclear. To overcome the problem of reverse causality, studies
have focused on the association between the MTHFR C677T polymorphism and AAA risk. However, the association is still inconsistent. Although 5 case–control studies [13–15,17,18] showed that carriers of the MTHFR 677T allele had an increased risk of AAA, 7 others [17,19,20,23–26] showed no significant association between these 2 factors. Furthermore, 4 studies [25,27–29] investigating this association using forest plots also provided conflicting results. The present study was designed to investigate the association between the MTHFR C677T polymorphism and AAA risk by performing a comprehensive meta-analysis, including a subgroup analysis.

2. Materials and methods

2.1. Publication search

Two independent investigators performed a comprehensive search for all studies on the association between the MTHFR C677T polymorphism and AAA risk in 2 electronic databases (PubMed and Embase) through March 31, 2016. We used the search terms “mthfr,” “methylene tetrahydrofolate reductase,” “5,10 methylene tetrahydrofolate reductase,” “677C,” “677T,” and “rs1801133” in combination with “aneurysm.” We searched for any additional studies in the references of all identified publications, including previous relevant meta-analyses. Unpublished data and supplemental information were also requested from authors. The search was restricted to studies in humans and articles published in English. This study protocol was approved by the ethics committee of Chinese PLA General Hospital.

2.2. Selection and exclusion criteria

Two investigators independently screened all titles and abstracts of the identified studies. Only studies published as full-length articles or letters in peer-reviewed journals were included. Studies included were in accordance with the following criteria: original case–control studies with matching control subjects; clinical trials studying the association between the MTHFR C677T polymorphism and AAA risk; all cases were diagnosed by ultrasound or computed tomography angiography; contained at least 2 comparison groups (AAA group and control group); all genotype distributions were reported in both case and control groups. Accordingly, the following exclusion criteria were also used: no controls; insufficient data reported (eg, abstracts, editorial, comments, reviews, and meta-analyses); and studies with duplicated data.

2.3. Data extraction and synthesis

For each study, data were extracted using a standard form by 2 independent authors. For each included study, the following information was collected: name of the first author; year of publication; country of origin, ethnicity, and sex of the participants; study design (source of control); numbers of cases and controls; mean age in case groups; prevalence of smoking in case groups; mean diameter of aneurysms; and numbers of CC, CT, and TT genotypes in cases and controls. In the event of a disagreement between authors, discrepancies of included studies were resolved by a third author.

2.4. Statistical analysis

We carried out this meta-analysis referring to PRISMA guidelines. The associations between the MTHFR C677T polymorphism and AAA were calculated as the pooled odds ratio (OR) with its corresponding 95% confidence interval (CI) in the allele contrast (T vs C), homozygote (TT vs CC), heterozygote (CT vs CC), recessive (TT vs CT + CC), and dominant (TT + CT vs CC) genetic models. The significance of the pooled OR was determined by the Z test, and a P value <0.05 was considered significant. We performed subgroup-analysis according to ethnicity (Caucasian or Asian), sex of the participants (females or not), source of control (hospital or population), mean age in case groups (≥70 years or <70 years), prevalence of smoking in case groups (≥60% or <60%), and mean diameter of aneurysm (≥55 mm or <55 mm).

Heterogeneity was assessed by the chi-square-based Cochran Q test and the I² statistic. Heterogeneity was regarded as statistically significant if PCH < 0.10 or I² > 50%. The random-effects model was used if the test of heterogeneity was significant. Otherwise, the fixed-effects model would be applied in the analysis. To assess the stability of the results, sensitivity analyses were performed to determine whether the exclusion of any studies could affect the results. The potential publication bias was primarily appraised by Begg funnel plot and further evaluated using the Egger test [30] with STATA 12.1 software (Stata Corporation, College Station, TX).

EpiData 3.1 (EpiData Association, Odense, Denmark) was used to gather initial data in a standard form, and Endnote X7 (Thomson Reuters [Scientific] Inc., Carlsbad, CA) was used for literature management. All statistical analyses were carried out primarily using the RevMan (RevMan 5.3 The Cochrane Collaboration, Oxford) and the STATA software version 12.1 (Stata Corporation, College Station, TX). All P values in the meta-analysis were 2-tailed, and P values <0.05 were considered significant.

3. Results

3.1. Characteristics of studies

Using the Pubmed and Embase databases, 119 studies were identified. After excluding 48 duplicates, 71 studies were identified for further evaluation. After title and abstract screening, 53 irrelevant studies were excluded. After assessing the remaining 18 full-text articles, 4 studies were excluded for insufficient data, and 2 for not being case–control studies (Fig. 1).

Ultimately, a total of 12 case–control studies [13–15,17,18,20–26] including 3671 cases and 6569 controls, were identified. The characteristics of the 12 included studies are presented in Tables 1 and 2. Ten studies [13–15,17,18,20–26] were based on Caucasian populations, and 2 studies [15,20] were based on Asian populations. Five studies [17,21–23,26] were population-based case–control studies, another 5 [13,15,22,24] were hospital-based, 11 [14] did not clarify the source of controls, and 1 [20] was a combination (hospital and population based). Ten studies [13,15,18,20–26] included both males and females and the remaining 2 [14,17] included only males. In 6 studies [14,15,20,22,23,25], the mean age of the case group was <70 years. In 5 studies [13–15,21,26], the prevalence of smoking in the case group was <60%. In 6 studies [13,15,21–23,25], the mean diameter of aneurysm was >55 mm.

3.2. Meta-analysis results

The frequency of the T allele varied widely across the 12 studies, ranging from 0.21 to 0.59 (Table 2). The average frequency of the T allele in overall populations was 0.37. There was a significant difference in frequency between Caucasians and Asians (0.34 vs 0.50, P < 0.01).
The main results of the meta-analysis are listed in Table 3. Overall, there was no association between the variant genotypes and AAA risk in different genetic models when all 12 studies were pooled into the meta-analysis, as shown in Table 3 and Fig. 2 (T vs C: OR = 1.12, 95% CI = 0.98–1.29, P = 0.10; TT vs CC: OR = 1.16, 95% CI = 0.91–1.47, P = 0.11; CT vs CC OR = 1.03, 95% CI = 0.99–1.08, P = 0.19; TT + CT vs CC: OR = 1.20, 95% CI = 0.98–1.47, P = 0.07; TT vs CT + CC: OR = 1.10, 95% CI = 0.89–1.35, P = 0.39). Ten studies[13,14,17,18,21–26], including 2937 cases and 5795 controls, were used to investigate the association in Caucasian populations. The results showed no association between the MTHFR C677T polymorphism and AAA risk in Caucasians using all 5 genetic models (Table 3 and Fig. 3). Two studies[15,20] were designed to investigate the association in Asians, which also showed no association in all 5 genetic models (Table 3 and Fig. 3).

Table 1
Characteristics of the studies included in the meta-analysis.

| First author | Publication year | Country | Ethnicity | Study design (case control) | Sex | Case number | Control number | Case age, y (mean ± SD) | Case smoking (N, %) | AAA diameter, mm (mean ± SD) |
|--------------|-----------------|---------|-----------|-----------------------------|-----|-------------|----------------|------------------------|-------------------|---------------------------|
| Brunelli     | 2000            | Italy   | Caucasian | NA                          | NF  | 58          | 60            | 69.3 ± 6.7             | 27 (47)           | NA                        |
| Strauss      | 2003            | Poland  | Caucasian | Population                 | WF  | 63          | 75            | 64.9 ± 7.9             | 34 (54)           | 60 ± 16                   |
| Soli         | 2005            | Italy   | Caucasian | Hospital                   | WF  | 438         | 438           | 74                      | 257 (59)          | 61 ± 13                   |
| Jones        | 2005            | New Zealand | Caucasian | Population                 | WF  | 428         | 282           | 71.7 ± 7.6             | NA                | 60.7 ± 16.5               |
| Ferrara      | 2006            | Italy   | Caucasian | Population                 | WF  | 88          | 44            | 62 ± 8.9                | NA                | 59.5 ± 15.4               |
| Giusti       | 2008            | Italy   | Caucasian | Hospital                   | WF  | 423         | 423           | 73.5*                  | 366 (87)          | 50*                       |
| Wong         | 2013            | Australia | Caucasian | Population                 | NF  | 617         | 3513          | 77.7                   | NA                | NA                        |
| Cao          | 2014            | China   | Asian     | Hospital                    | WF  | 463         | 463           | 67.7 ± 10.5            | 213 (46)          | 56.2 ± 15.6               |
| Scuillman    | 2014            | America | Caucasian | Population                 | WF  | 141         | 168           | 71.2 ± 0.96            | 40 (28)           | 51.3 ± 9.7                |
| Saratis_Greece | 2015       | Greece  | Caucasian | Hospital                   | WF  | 397         | 393           | 69 ± 8                 | 290 (73)          | 62 ± 1.4                  |
| Carattes_UK  | 2015            | UK      | Caucasian | Hospital                   | WF  | 400         | 400           | 72 ± 7                 | 360 (90)          | 54 ± 10                   |
| Liu          | 2016            | China   | Asian     | Population + Hospital       | WF  | 155         | 310           | 69.18 ± 9.94           | 132 (65)          | 64.18 ± 16.8              |

AAA = abdominal aortic aneurysm, NF = no females, WF = with females.
* Median of age.
† Median of Diameter.
The subgroup meta-analyses are shown in Table 4. Six studies with mean age <70 years old in the case group, including 1115 cases and 1345 controls, showed a significant association between the MTHFR C677T polymorphism and AAA risk in the dominant model (TT+CT vs CC: OR = 1.73, 95% CI = 1.10–2.12, P = 0.02). Five studies with prevalence of smoking in the case group <60, including 1163 cases and 1204 controls, showed a significant association in the dominant model (TT+CT vs CC: OR = 1.39, 95% CI = 1.02–1.90, P = 0.04). Six studies with AAA diameter ≥55mm, including 1768 cases and 1695 controls, showed a significant association based on the dominant models (TT+CT vs CC: OR = 1.55, 95% CI = 1.07–2.24, P = 0.02).

3.3. Publication bias

A Begg funnel plot and an Egger test were performed to assess the publication bias. As shown in Fig. 4, the funnel plots did not reveal any obvious asymmetry in overall population, and the results of Egger test revealed no publication bias (P > 0.05).

4. Discussion

HHcy is an independent risk factor for the development of atherosclerosis, cardiovascular disease, and stroke. However, the results of previous studies that investigated the relationship between HHcy and AAA are inconsistent. Whether HHcy plays a direct causal role in the pathogenesis of AAA remains elusive. To overcome the problem of reverse causality, several studies sought an association between MTHFR genotype and AAA risk. However, the association between the MTHFR C677T polymorphism and AAA is still controversial.

In the present meta-analysis with 3555 cases and 6568 controls from 12 independent studies, no significant association was detected between the MTHFR C677T polymorphism and AAA

### Table 2

| First author | Cases | Controls | Allele frequency (N, %) |
|--------------|-------|----------|------------------------|
|              | CC    | CT       | TT         | C     | T     | MAF     | C     | T     | MAF     |
| Brunelli     | 58    | 14       | 32         | 12    | 60    | 19      | 35    | 6     | 60      |
| Strauss      | 63    | 21       | 38         | 4     | 75    | 49      | 20    | 6     | 80      |
| Sofi         | 438   | 141      | 217        | 80    | 438   | 166     | 211   | 61    | 499     |
| Jones        | 428   | 210      | 169        | 49    | 282   | 134     | 122   | 26    | 589     |
| Ferrara      | 88    | 28       | 36         | 4     | 92    | 33      | 10    | 1     | 112     |
| Giusti       | 423   | 139      | 206        | 78    | 423   | 109     | 214   | 100   | 484     |
| Wong         | 617   | 281      | 267        | 69    | 551   | 149     | 156   | 398   | 829     |
| Cao          | 463   | 138      | 235        | 90    | 463   | 156     | 252   | 55    | 511     |
| Duellman     | 141   | 66       | 53         | 22    | 168   | 79      | 68    | 21    | 165     |
| Saratzis, Greece | 397 | 121    | 132        | 35    | 393   | 170     | 164   | 59    | 374     |
| Saratzis, UK | 400   | 180      | 166        | 47    | 400   | 200     | 160   | 39    | 526     |
| Liu          | 155   | 30       | 77         | 48    | 310   | 65      | 125   | 120   | 137     |

MAF = minor allele frequency.

### Table 3

Meta-analysis of the association between MTHFR C677T polymorphism and abdominal aortic aneurysm risk based on different models.

| Comparisons | OR     | 95% CI  | P value | P %   | P value | Effects model |
|-------------|--------|---------|---------|-------|---------|---------------|
| T vs C      | 1.12   | 0.98–1.29 | 0.10   | 73    | <0.0001 | Random        |
| Overall     | 1.14   | 0.97–1.34 | 0.11   | 75    | <0.0001 | Random        |
| Caucasian   | 1.07   | 0.75–1.53 | 0.70   | 78    | 0.03    | Random        |
| Asian       | 1.16   | 0.91–1.47 | 0.23   | 57    | 0.007   | Random        |
| Overall     | 1.11   | 0.86–1.43 | 0.41   | 51    | 0.03    | Random        |
| TT vs CC    | 1.30   | 0.62–2.72 | 0.49   | 79    | 0.03    | Random        |
| Overall     | 1.03   | 0.98–1.08 | 0.29   | 74    | <0.0001 | Random        |
| Caucasian   | 1.04   | 0.95–1.14 | 0.35   | 0     | 0.47    | Fixed         |
| Asian       | 1.20   | 0.96–1.47 | 0.07   | 75    | <0.0001 | Random        |
| Overall     | 1.23   | 0.97–1.57 | 0.09   | 79    | <0.0001 | Random        |
| TT vs CC    | 1.17   | 0.92–1.49 | 0.19   | 0     | 0.78    | Fixed         |
| Overall     | 1.10   | 0.89–1.35 | 0.39   | 55    | 0.01    | Random        |
| Caucasian   | 1.04   | 0.90–1.20 | 0.62   | 30    | 0.17    | Fixed         |
| Asian       | 1.13   | 0.46–2.80 | 0.79   | 91    | 0.001   | Random        |

CI = confidence interval, MTHFR = methylenetetrahydrofolate reductase.
risk in the overall population in all 5 genetic models. Additionally, no significant association was revealed within Caucasian or Asian subpopulations. However, the subgroup meta-analysis showed a significant association between the MTHFR C677T polymorphism and AAA risk in the subgroups of cases with a mean age <70 years, prevalence of smoking <60%, and AAA diameter ≥55 mm in the dominant genetic model. The results suggest that age, smoking, and AAA diameter may play a role in the relationship between the MTHFR C677T polymorphism and AAA risk.

Although 4 studies\(^{25,27-29}\) using forest plots investigated the association between the MTHFR C677T polymorphism and AAA risk, the results of these studies were controversial and lacked a subgroup analysis. Three meta-analyses\(^{25,27,28}\) showed that carriers of the MTHFR 677T allele presented with an increased risk of AAA. The study by Thompson et al.\(^{27}\)
including 1075 cases and 1067 controls from 5 independent studies, revealed a significant effect of the T allele variant in increasing the risk of AAA (risk ratio = 1.14, 95% CI = 1.08–1.21). McCollan et al.\(^{28}\) including 817 cases and 629 controls from 6 studies (including 3 studies with the same author indicating a potential duplication of data), showed a similar significant result (TT vs CC, OR = 1.34, 95% CI = 1.08–1.65). Saratzis et al.\(^{14,25}\) including 2498 cases and 6212 controls from 9 studies, also showed a significant OR between the MTHFR C677T polymorphism and AAA (OR = 1.07, 95% CI = 1.02–1.12). The meta-analysis\(^{29}\) by Bradley et al., including 2498 cases and 6212 controls from 9 studies, showed no significant association between the MTHFR C677T polymorphism and AAA (OR = 1.07, 95% CI = 1.02–1.12). Our subgroup meta-analysis of 6 studies\(^{13,15,20,22,23}\) with a mean age <70 years in case groups, showed a significant association between the MTHFR C677T polymorphism and AAA risk in the dominant model (TT + CT vs CC, OR = 1.72, 95% CI = 1.60–1.84, \(P = 0.01\)). Ferrara et al.\(^{22}\) divided the patients of the AA group into 2 groups according to age and determined that the frequency of the 677T allele in younger patients with AAA was significantly higher than that in older patients with AAA. Our subgroup meta-analysis of 5 studies\(^{13,15,21,23,26}\) of cases with prevalence of smoking <60% also showed a significant association between the MTHFR C677T polymorphism and AAA risk (TT + CT vs CC, OR = 1.39, 95% CI = 1.02–1.90, \(P = 0.04\)). Strass et al.\(^{32}\) divided the patients of the AA group into 2 groups—those who smoke and those who do not—and showed that the frequency of the 677T allele in patients with AAA who smoke was higher than that in patients with AAA who do not, but this was not significant. In our subgroup meta-analysis of 6 studies\(^{13,15,21–23,25}\) of AAA with a diameter \(\geq 55\) mm, a significant association between the MTHFR C677T polymorphism and AAA risk was observed (TT + CT vs CC: OR = 1.55, 95% CI = 1.07–2.24, \(P = 0.02\)). Jones et al.\(^{23}\) showed AAA diameter was significantly greater in T homozygotes compared to that in C allele carriers and the OR for T homozygotes and aneurysm size was 1.35 (95% CI, 1.05–1.72, \(P = 0.02\)). However, 4 other studies\(^{13,15,21,24}\) indicated that the aneurysm diameter was not significantly larger in the AAA patients with the MTHFR 677TT polymorphism than in those with the MTHFR 677CC polymorphism. Our previous study\(^{20}\) also showed no significant association between the MTHFR C677T allele and aneurysm diameter with no significantly higher increase in aneurysm size in patients with the CT or TT genotype than in those with the CC genotype. Interestingly, in our previous

### Table 4

| Subgroups | Genotype (N) | Effects value (95% CI) | \(P\) value | \(I^2\) | \(df\) | \(P\) value | Effects model |
|-----------|-------------|------------------------|-------------|-------|-------|-------------|--------------|
| Age in cases, y (mean) | | | | | | | |
| <70 | 1616 | 844 | 1.73 | 1.10–2.12 | 0.02 | 81 | 5 | <0.0001 | Random |
| \(\geq 70\) | 412 | 380 | 1.06 | 0.88–1.27 | 0.56 | 0 | 2 | 0.52 | Fixed |
| Sex | | | | | | | |
| With females | 3640 | 2235 | 1.25 | 0.98–1.60 | 0.07 | 78 | 9 | <0.0001 | Random |
| No females | 2385 | 1863 | 0.96 | 0.81–1.14 | 0.64 | 5 | 1 | 0.30 | Fixed |
| Study design | | | | | | | |
| HB | 2601 | 1520 | 1.07 | 0.87–1.31 | 0.52 | 61 | 4 | 0.04 | Random |
| PB | 2969 | 2450 | 1.61 | 0.97–2.67 | 0.06 | 88 | 4 | <0.0001 | Random |
| Smoking in case (%) | | | | | | | |
| <60 | 1518 | 849 | 1.39 | 1.02–1.90 | 0.04 | 61 | 4 | 0.03 | Random |
| \(\geq 60\) | 1770 | 1014 | 0.99 | 0.77–1.26 | 0.91 | 56 | 3 | 0.08 | Random |
| AAA diameter, mm (mean) | | | | | | | |
| <55 | 546 | 260 | 1.13 | 0.91–1.40 | 0.26 | 0 | 2 | 0.0002 | Fixed |
| \(\geq 55\) | 2096 | 1367 | 1.55 | 1.07–2.24 | 0.02 | 83 | 5 | <0.0001 | Random |

AAA = abdominal aortic aneurysm, CI = confidence interval, HB = hospital based, MTHFR = methylenetetrahydrofolate reductase, OR = odds ratio, PB = population based.
study,[20] there was a significant association between the MTHFR 677T allele and the risk of AAA (OR = 2.46; 95% CI = 1.10–5.50; \( p = 0.03 \)) in the subgroup of patients who consumed alcohol, indicating that consuming alcohol may play an important role in the association between the MTHFR 677T polymorphism and AAA. These results indicate that other factors may play a role in the association between the MTHFR 677T polymorphism and AAA. Additional studies focusing on the association between the MTHFR C677T polymorphism and AAA taking into account confounding factors and their interactions as well as subgroup analyses are needed to clarify these findings.

Our study provides evidence of the association between the MTHFR C677T polymorphism and AAA risk by performing a comprehensive meta-analysis. When interpreting our findings, several limitations should be considered. First, only 2 of the included studies analyzed Asian populations and no study data from ethnicities other than Caucasian and Asian populations were included. Thus, additional studies with large sample sizes could be warranted in the future to address the lack of available data and could be addressed in future studies. Finally, our main analysis was based on unadjusted estimates of ORs owing to the lack of available data and could be adjusted in future studies including different ethnicities.

In summary, our present meta-analysis provides evidence of the association between the MTHFR C677T polymorphism and AAA risk, and suggests that the MTHFR T allele increases the risk of AAA in younger, nonsmoking, larger-AAA-diameter subgroups of patients. Future studies, including different subgroup analyses, are warranted to verify our findings.

5. Conclusions

In summary, our present meta-analysis provides evidence of the association between the MTHFR C677T polymorphism and AAA risk, and suggests that the MTHFR T allele increases the risk of AAA in younger, nonsmoking, larger-AAA-diameter subgroups of patients. Future studies, including different subgroup analyses, are warranted to verify our findings.

References

[1] Thompson RW. Detection and management of small aortic aneurysms. New Engl J Med 2002;346:1484–6.
[2] Forsdahl SH, Singh K, Solberg S, et al. Risk factors for abdominal aortic aneurysms: a 7-year prospective study: the Tromso Study, 1994-2001. Circulation 2009;119:2202–8.
[3] Lederle FA, Johnson GR, Wilson SE, et al. Yield of repeated screening for abdominal aortic aneurysm after a 4-year interval. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. Arch Intern Med 2000;160:1117–21.
[4] Bird AN, Davis AM. Screening for abdominal aortic aneurysm. JAMA 2015;313:1156–7.
[5] Le MT, Jamrozik K, Davis TM, et al. Negative association between infrarenal aortic diameter and glycaemia: the Health in Men Study. Eur J Vasc Endovasc Surg 2007;33:599–604.
[6] Radak D, Tanaskovic S, Katski N, et al. Protective role of diabetes mellitus on abdominal aortic aneurysm pathogenesis: myth or reality? Curr Vasc Pharmacol 2015.
[7] Weintrob NL. Understanding abdominal aortic aneurysm. New Engl J Med 2009;361:1114–6.
[8] Liu Z, Luo H, Zhang L, et al. Hyperhomocysteinemia exaggerates advenital inflammation and angiogenesis II-induced abdominal aortic aneurysm in mice. Circ Res 2012;111:1261–73.
[9] Casas JP, Bautista LE, Smeeth L, et al. Homocysteine and stroke: evidence on a causal link from mendelian randomisation. Lancet 2005;365:224–32.
[10] Klerk M, Verhoef P, Clarke R, et al. MTHFR 677C>T polymorphism and risk of coronary heart disease: a meta-analysis. JAMA 2002;288:2023–31.
[11] Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002;325:1202.
[12] Bautista LE, Arenas IA, Penuela A, et al. Total plasma homocysteine level and risk of cardiovascular disease: a meta-analysis of prospective cohort studies. J Clin Epidemiol 2002;55:882–7.
[13] Sofi F, Marascu R, Giusti B, et al. High levels of homocysteine, lipoprotein (a) and plasminogen activator inhibitor-1 are present in patients with abdominal aortic aneurysm. Thromb Haemost 2005;94:1094–8.
[14] Brunelli T, Prisco D, Fedi S, et al. High prevalence of mild hyperhomocysteinemia in patients with abdominal aortic aneurysm. J Vasc Surg 2000;32:531–6.
[15] Cao H, Hu X, Zhang Q, et al. Hyperhomocysteinemia, low folate concentrations and MTHFR C677T mutation in abdominal aortic aneurysm. Vasa 2014;43:181–8.
[16] Spark JI, Laws P, Fitridge R. The incidence of hyperhomocysteinemia in vascular patients. Eur J Vasc Endovasc Surg 2003;26:558–61.
[17] Wong YY, Colledge J, Flicker L, et al. Plasma total homocysteine is associated with abdominal aortic aneurysm and aortic diameter in older men. J Vasc Surg 2013;58:364–70.
[18] Peeters AC, van Landeghem BA, Graafsma SJ, et al. Low vitamin B6, and not plasma homocysteine concentration, as risk factor for abdominal aortic aneurysm: a retrospective case-control study. J Vasc Surg 2007;45:701–5.
[19] Lindqvist M, Hellstrom A, Henriksson AE. Abdominal aortic aneurysm and the association with serum levels of Homocysteine, vitamins B6, B12 and Folate, Am J Cardiovad Surg 2012;2:318–22.
[20] Liu J, Wei Zuo S, Li Y, et al. Hyperhomocysteinemia is an independent risk factor of abdominal aortic aneurysm in a Chinese Han population. Sci Rep 2016;6:17966.
[21] Strauss E, Waliszewski K, Gabriel M, et al. Increased risk of the abdominal aortic aneurysm in carriers of the MTHFR 677T allele. J Appl Gen 2003;44:85–93.
[22] Ferrara F, Novo S, Girmaud S, et al. Methylene tetrahydrofolate reductase mutation in patients with abdominal aortic aneurysms subdivided for age. Clin Hemorheol Microcirc 2006;34:421–6.
[23] Jones GT, Harris EL, Phillips LV, et al. Genetic analysis of 36 polymorphisms in 17 genes involved in methionine metabolism in patients with abdominal aortic aneurysm. J Med Gen 2008;45:721–30.
[24] Saratzis A, Bowen MJ, Wild B, et al. Association between seven single nucleotide polymorphisms involved in inflammation and proteolysis and abdominal aortic aneurysm. J Vasc Surg 2015;61:1120–8, e1121.
[25] Duellman T, Warren CL, Matsumura J, et al. Analysis of multiple genetic polymorphisms in aggressive-growing and slow-growing abdominal aortic aneurysms. J Vasc Surg 2014;60:613–21, e613.
[26] Thompson AR, Drenos F, Hafez H, et al. Candidate gene association studies in abdominal aortic aneurysm disease: a review and meta-analysis. Eur J Vasc Endovasc Surg 2008;35:19–30.
[27] McGolran P, Peck GE, Greenhalgh RM, et al. The genetics of abdominal aortic aneurysms: a comprehensive meta-analysis involving eight candidate genes in over 16,700 patients. Int J Sci 2009;94:350–8.
[28] Bradley DT, Badger SA, McFarland M, et al. Abdominal aortic aneurysm genetic associations: mostly false? A systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2016;51:64–75.
[29] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[30] Warsi AA, Davies B, Morris-Stiff G, et al. Abdominal aortic aneurysm and its correlation to plasma homocysteine, and vitamins. Eur J Vasc Endovasc Surg 2004;27:75–9. 
[31] Strauss E, Waliszewski K, Pawlak AL. The different genotypes of MTHFR 1298A>C and PON1-108C>T polymorphisms confer the increased risk of the abdominal aortic aneurysm in the smoking and nonsmoking persons. Przegląd lekarski 2005;62:1023–30.