The Genetic Risk Of Methylene Tetrahydrofolate Reductase Single Nucleotide Polymorphism On Blood Homocysteine is Dependent On Sex, Race and Supplement Use - a Systematic Review and Meta Analysis

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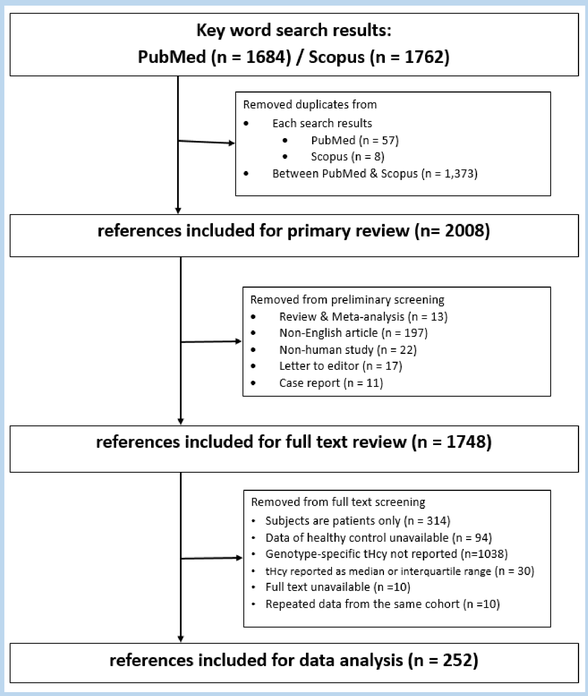
Overview

- The *MTHFR* C667T (rs1801133) polymorphism has been widely accepted as a risk marker of elevated blood homocysteine (tHcy) [1], and has been used in genetic testing for risk prediction. Yet, there is a lack of consistency in terms of the penetrance and effect size of this genetic variant.
- There are reports of effect modifiers on rs1801133, such as age, sex, race, supplement use, smoking, alcohol drinking, etc[2-4]. However, the results are inconsistent and few studies reported how the covariates affect tHcy collectively.
- There are few studies that investigated how rs1801133 contributes the risk of hyperhomocysteinemia in combination with other covariates.
- It is challenging to study the effect of rs1801133 with exhaustive inclusion of all covariates. Meta analysis offers a good alternative by combing data available in the literature.

Methods

- A thorough literature review to gather data from available publications that report the effect of rs1801133 on tHcy.
- Extract the association results of tHcy and rs1801133, along with potential covariates.
- Stratify the genetic association result based on the inclusion status of potential covariates.
- Analyze stratified data by linear multivariate regression and fully hierarchical moderator analysis.

❖ **Flow Chart**



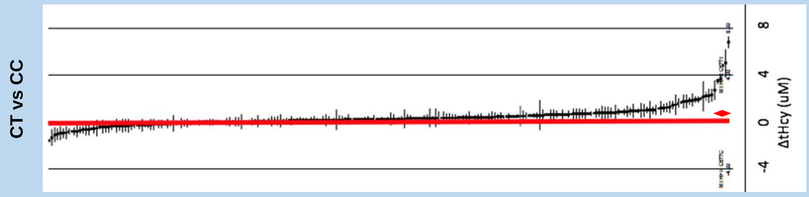
Results

1. Characteristics of Homocysteine Levels for Each Genotyping in Three Different Models(Table 1)

Model	No. of Articles	N Total	CC_N	CC_Mean (SD)	CT_N	CT_Mean (SD)	TT_N	TT_Mean (SD)
OverAll	252	137428	67615	9.61 (1.52)	53810	9.9 (1.48)	16003	11.95 (1.61)
Meta Regression	115	64242	28067	9.64 (1.4)	27831	10.16 (1.43)	8344	12.2 (1.53)
Fully Hierarchical Moderator Analysis	41	8559	3498	8.52 (1.18)	3632	8.39 (1.04)	1429	10.01 (1.52)

2. The Effect of rs1801133 on tHcy in General Population is Highly Heterogeneous

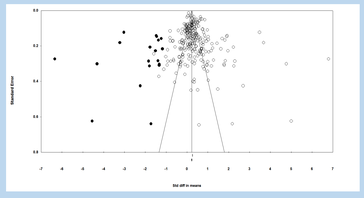
❖ **Figure 1 Overall Forest Plot and Funnel Plot**



Heterogeneity: Tau²=0.191, Q=4391; df=241 (p<0.0001); I²=95; **Test for overall effect:** Z=12 (p<0.0001)

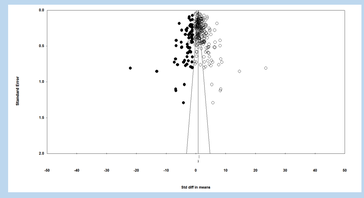
Heterogeneity: Tau²=1.421, Q=12794; df=236 (p<0.0001); I²=98; **Test for overall effect**: Z=23 (p<0.0001)

CT vs CC



Egger's Regression Intercept: t-value=3; df=240 (p=0.00233)

TT vs CC



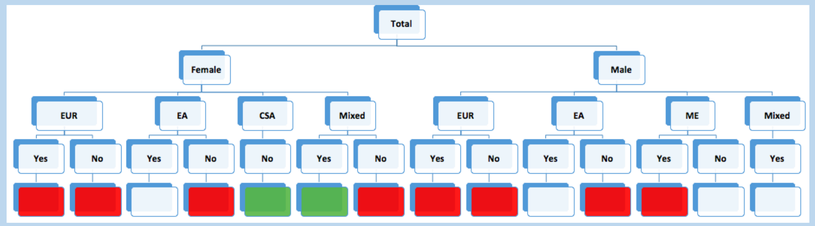
Egger's Regression Intercept: t-value=6; df=235 (p<0.000001)

3. Gender, race and Supplement Use Affect the Effect of rs1801133 on tHcy Significantly

❖ **Table 2 Regression Analysis of Effect Modifiers of rs1801133 Risk**

	ΔtHcy (TT vs CC)		
Variables	Estimate (μM)	95% CI	P Value
Sex (Female vs Male)	-1.28	(-2.01, -0.55)	0.001
Race (Central/South Asia vs Mixed)	3.56	(0.85, 6.32)	0.013
Supplement (Yes vs No)	-1.22	(-2.11, -0.32)	0.012

❖ **Figure 2 Fully Hierarchical Matrix of ΔtHcy**



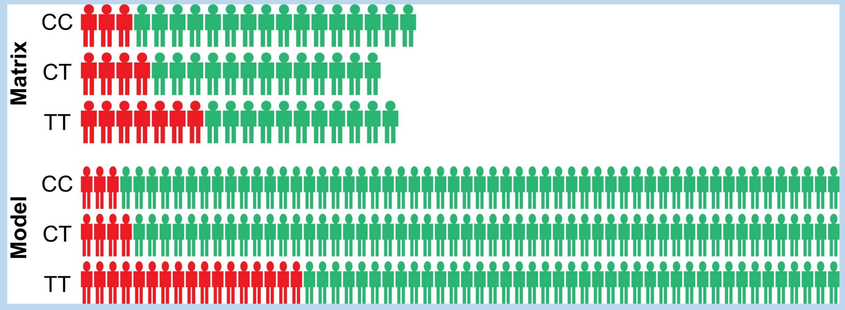
Race: EUR(European); EA(East Asia); CSA(Central/South Asia); ME(Middle East); Mixed(Mexican, African American, Others)
Supplement: No (No Food Fortification); Yes (Food Fortification or No Food Fortification & Supplement Use)

4. Gender, Race, and Supplement Use Significantly Affect the rs1801133 Risk on tHcy.

❖ **Table 3 Regression Analysis of Variables That Affect tHcy**

Variables	Estimate(μM)	95% CI	P Value
Age (Older Adult vs Childhood)	3.68	(2.16, 5.19)	<0.0001
Age (Young Adult vs Childhood)	2.36	(0.94, 3.77)	0.0013
Sex (Female vs Male)	-2.02	(-2.78, -1.26)	<0.0001
Race (Central/South Asia vs Mixed)	4.28	(2.29, 6.27)	<0.0001
Race (Africa vs Mixed)	3.91	(0.95, 6.88)	0.01
Supplement (Yes vs No)	-1.67	(-2.32, -1.01)	<0.0001
Smoking (Nonsmoker vs Mixed)	-2.24	(-3.23, -1.24)	<0.0001
rs1801133 (CT vs CC)	0.47	(0.22, 0.71)	0.0003
rs1801133 (TT vs CC)	2.46	(2.19, 2.73)	<0.0001

❖ **Figure 3 Regression Model and Fully Hierarchical Analysis of tHcy**



Conclusions

- It is important to predict the effect of rs1801133 on tHcy under the context of the multiple covariates.
- Well-designed statistical analyses based on the available data are also necessary for this purpose.

References

1. Holmes MV et al. Effect modification by population dietary folate on the association between MTHFR genotype, homocysteine, and stroke risk -a meta-analysis of genetic studies and randomised trials. *Lancet.* 2011;378(9791):584-94.
2. Tsai MY et al. Polygenic association with total homocysteine in the post-folic acid fortification era: the CARDIA study. *Molecular genetics and metabolism.* 2009;98(1-2):181-6.
3. Russo GT, et al. Age and gender affect the relation between methylenetetrahydrofolate reductase C677T genotype and fasting plasma homocysteine concentrations in the Framingham Offspring Study Cohort. *The Journal of nutrition.* 2003;133(11):3416-21.