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Meta-analysis demonstrates Gly482Ser variant of PPARGC1A is associated with components of metabolic syndrome within Asian populations

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List of Tables and Figures

Abstract:

Aim: To determine the association of peroxisome proliferator activated receptor gamma coactivator 1 Gly482Ser variant with components of metabolic syndrome.

Materials and Methods: A systematic search was carried out using Web of Science, PubMed, EMBASE and the Cochrane library using the key words: Peroxisome proliferator activator receptor gamma coactivator 1, PPARGC1A, PGC-1, PGC-1alpha, and PGC1alpha alone or with polymorphism, Gly482Ser and rs8192678.

Results: Data from 19 articles generated 28 separate data sets. Under the recessive model fasting plasma glucose was significantly lower in AA genotypes when compared to GG+GA in the total sample group and in non-Asian group ($p<0.001$). The AA genotype showed significantly lower levels of total cholesterol compared to GG+GA genotype using the recessive model with the non-Asian group ($p<0.05$). Under the dominant model, body mass index of the GG genotype was significantly higher in Asian subgroups ($p<0.05$)

Conclusion: PPARGC1A Gly482Ser variant impacts differently in Asian population groups.

Keywords:

Metabolic syndrome, PPARGC1A, meta-analysis, Gly482Ser, single nucleotide polymorphism

1. Introduction

Metabolic syndrome is the combined presentation of at least three of the following criteria: impaired fasting glucose, increased waist circumference, elevated blood pressure (BP), elevated triglycerides and/or elevated cholesterol [1] (Supplementary Table 1). In this study we will investigate the association of components of metabolic syndrome with a genetic variant (Gly482Ser) of the peroxisome proliferator activated receptor co-activator 1A (PPARGC1A). PPARGC1A interacts with PPAR gamma and this facilitates interaction with multiple transcription factors [2]. PPARGC1A plays a vital role, directly or indirectly in lipid metabolism and it is responsible for the activation of farnesoid X receptor (FXR), which decreases the level of triglycerides in the liver [3]. It also regulates the activity of the human hepatic lipase gene (LIPC) which is involved in lipid metabolism [4]. Furthermore, the expression of PPARGC1A in conjunction with its nuclear receptor, hepatocyte nuclear factor 4α (HNF4α) in the liver, increases a range of apolipoproteins that are responsible for triglyceride metabolism and very low-density lipoprotein (VLDL) metabolism [5]. PPARGC1A plays a major role in glucose transport in skeletal muscle [6] and pancreatic beta-cells [7] and co-activates the cholesterol 7-α-hydroxylase (CYP7A1) gene that encodes an enzyme essential for cholesterol metabolism [8,9].
Located on chromosome 4p15.1 [10], the gene has a number of single nucleotide polymorphisms and in this study, we will explore the association of the missense variant Gly482Ser (rs8192678) of PPARGC1A with lipid profile and components of metabolic syndrome. G is the major allele and A is the minor allele resulting in either glycine or serine amino acid residue at codon 482 of PPARGC1A. The minor allele remains the same in most populations although the incidence within the Tongan population was over 70% [11]. This single nucleotide polymoyphism (SNP) lies within exon 8 of the gene and correlates with a region known to interact with PPARγ [10]. The variant of this SNP influences the age-dependent expression of the PPARGC1A gene in skeletal muscle [12] and has also been associated with an increase in body fat mass, body fat ratio and body mass index (BMI) in Korean children [13] and in a Mexican population [14]. Hyperinsulinemia and an increased insulin resistance index in Chinese adults have also been noted [15]. Furthermore, there is an association of this genotype with excess weight gain in male subjects with Type 1 diabetes mellitus (T1DM) reported in a predominately Caucasian population

[16] although the minor allele did not show any association with metabolic syndrome in Danish populations [17] or with body fat mass in an Indian population [18]. This allele has also been associated with hypertension in young individuals [19], high blood pressure in middle-aged men [20], and in men with Type 2 diabetes [21]. In contrast, a reduced risk of hypertension was observed in Danish Caucasians with the minor allele [22].

The Gly482Ser polymorphism has been variously associated with lipid profile. A reduced clearance of non-esterified fatty acid following a glucose load was reported in a European population with carriers of the Gly482Ser allele [23] while in a group of participants from the Middle East, total cholesterol and LDL level were found to be significantly higher in the wildtype [24]. Normoglycemic individuals from a Kurdish-Iranian population carrying the GA+AA genotype had lower levels of high-density lipoprotein (HDL) when compared to the GG genotype [25]. The levels of triglycerides (TG) in the pre-obese and obese group were significantly higher in wildtype genotypes of Gly482Ser under a dominant genetic model in a Mexican population [14]. Other studies such as, Andrulionyte et al, 2004 [26]; Zhang et al, 2007 [27]; Goyenechea et al, 2008 [28] and Niktin et al., 2010 [29] failed to show any significant difference in the levels of serum lipids in different genotype groups. Furthermore, due to conflicting results regarding Gly482Ser association with lipid levels and the importance of lipid profile and BMI in metabolic syndrome, this study aimed to assess if an association of the Gly482Ser polymorphism with lipid profile occurs. A meta-analysis was conducted to address inconsistencies in the literature and to determine if further insights into the role of this variant can be derived in association with biochemical and metabolic characteristics. The null hypothesis is therefore that the genetic variant Gly482Ser is not associated with components of metabolic syndrome.

2. Material and Methods

2.1. Literature Search strategy

The literature search strategy used is consistent with the guidelines outlined for the PRISMA [30]. An electronic search of the relevant published articles was conducted using web of science ((http://apps.webofknowledge.com), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE and the Cochrane library. All original research articles published before 28/05/2018 were identified independently by two investigators using keywords specified in Supplementary Table 1, Any inconsistencies were discussed and articles selected according to the following inclusion criteria: full original research articles; published in the English language; conducted on humans; included genotype data related to rs8192678 (Gly482Ser) and corresponding biological data (TC, TG, HDL and LDL). If these criteria were satisfied, corresponding biological data such as BMI and fasting plasma glucose (FPG) concentration were also included. All articles represented either a case-control study, a cross-sectional study or an intervention study. If an intervention study was included; only the data prior to the intervention were selected to avoid any bias from the intervention itself. Articles were excluded if the reported data was presented as an interquartile range, contained data for those under 18 years of age or for those participants who were overtly taking statins. In some studies, it is recognised that some participants may be taking a range of medications that are not reported and this may cause a degree of bias.

2.2 Data extraction

The following information was obtained from the selected peer reviewed articles: authors (articles recorded as first author et al., and year of publication) ethnicity of subjects, mean age, gender ratio, body mass index, sample size, mean value of high-density lipid (HDL), low density lipid (LDL), total cholesterol (TC), tri-glycerides (TG), and fasting plasm glucose (FPG) concentrations with the corresponding genotypes along with standard deviation. In order to provide uniform measurement units, plasma lipids expressed in mg/dl were converted into mmol/L; the following conversion factor was used for HDL, LDL and TC; 1mmol/L is equivalent to 38.6mg/dl) for TG; 1 mmol/L is equivalent to 88.5mg/L; and for glucose, 1mmol/L is equivalent to 18.01 mg/L..

If more than one data set was found within a single published article, they were treated as distinct data under the same author with appropriate qualification of distinction of the data. If the sample

size varied with each lipid variable as in the case of Vohl et al, (2005) [31], the lowest possible sample size was considered. When the lipid levels in three genotype groups were available, the mean and standard deviation of the two genotypes were combined to analyse the data under either the dominant or the recessive genetic models. The dominant genetic model assumes that the heterozygous and the homozygous form of the gene are treated as a single category and compared to homozygous dominant genotype while the recessive model compares the combined heterozygote and homozygous dominant forms to the homozygous recessive genotype. The two data sets from Okauchi et al, 2008 [32] representing male and female subjects with or without type 2 diabetes have been combined into one single group.

2.3 Statistical analysis

Meta-analysis was performed using STATA 13.1 (StataCorp. 2013. *Stata Statistical Software: Release 13*). The "Metan": command of the STATA 13.1 was used for the present meta-analysis. All data are presented as mean ± SD and all the p-values were two-sided unless otherwise stated and a p-value ≤ 0.05 was regarded as statistically significant.

The pooled weighted mean difference (WMD) with 95% confidence interval (CI) was used for the meta-analysis and the heterogeneity of the data was determined using the Chi-squared based Q-test and I^2 (0-100%) statistics. The criteria for rejecting the null hypothesis of homogeneity was 10% ($p<0.1$). The Random effect model [33] was used when there was significant heterogeneity within the study data and the fixed effect model [34] was used when there was no significant heterogeneity. Heterogeneity was measured using Cochran's Q. This follows a chi-squared distribution with k-1 degrees of freedom, where k is the number of studies carried out.

Meta-analysis of the genotype data was initially carried out on the total selected data and subsequently separated to compare the data from Asian or Non-Asian sources. In addition, the effect size of the biochemical data for each of the sub-groups was calculated using Cohen's *d* and results are presented as either a "small" or a "medium" effect based on Cohen's criteria, where a Small effect = 0.2; Medium effect = 0.5; large effect = 0.8 [35]. The dominant and recessive models were carried out with the dominant model comparing the GG genotype with GA and AA, whereas the recessive genetic model compared the AA genotype with GG and GA. It was not

possible to carry out an analysis of codominance as the articles did not consistently present the heterozygote genotype (GA) as an independent variable.

3. Results:

3.1 Study characteristics

A total of 850 articles were identified from the initial search (Fig. 1) with 291 articles from Web of Science, 241 from Pub med, 309 from EMBASE and 9 from the Cochrane library. Articles that were either not relevant, in that they did not include relevant data or were not in English or were not studied in the human population, were excluded leaving 29 relevant articles for further scrutiny. Of these articles, 10 were excluded based on the following criteria: either the data were not from the original source (e.g. meta-analysis) (n=4), the participants were taking statins (n=1), subjects younger than 18 years (n=3) were excluded, the genotype data was presented as inter-quartile range, or there was concern about inaccuracies and/or inconsistencies in the presentation of the data (n=1) or only interquartile genotype data was reported (n=1). Of the remaining 19 articles, some included more than one data set and therefore the final selection contained 28 data sets representing 7492 subjects (Fig. 1).

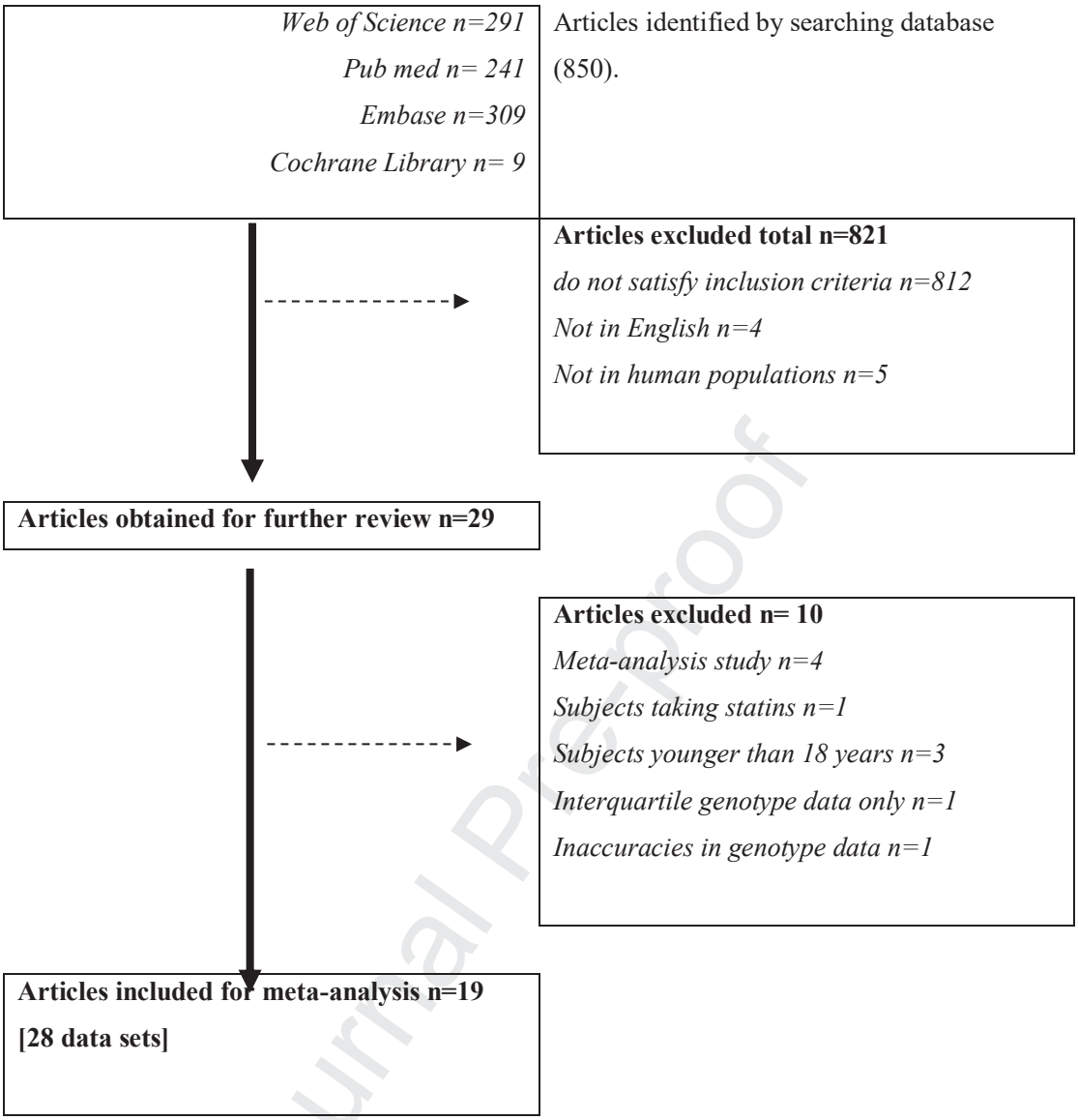


Figure 1: Flow chart showing the systematic screening and selection process of articles used in this study.

Articles published between 2001 and 2018 included data relating to subjects from North, South and Central America, the Middle East, Europe, Asia and from an ethnically mixed population group (Table 1). The weighted mean age for the total group was 48years (± 9.8) although age data was not available for the Ambye et al. study [17]. The study participants were separated for some of the analyses based on whether they were from an Asian or a non-Asian background and the weighted mean age did not change (48 years) with a weighted standard deviation of 14.35 and 16.26 for the Asian and the non-Asian group respectively.

The data sets were combined across the studies and values of TC, HDL, LDL, TG, BMI and FPG are presented (Table 1). The association of lipid profile, FPG and BMI with genotype, GG, GA or

AA was then determined, and a summary of the complete data analysis is presented in Table 2. The data is presented as either wildtype (GG) or carrier (GA or AA) and analysis was based on the dominant or the recessive model. The data available from the articles selected were not in an appropriate format to carry out determination of co-dominance as the number of articles with data separating the GA and AA genotypes was not of sufficient power to conduct the analysis. The effect size of the lipid profile data for the two groups was determined using Cohen's criteria: where a "small effect" was evident for HDL and TG at -0.26, -0.17 respectively; with a medium effect size of 0.63 recorded for TC in the Asian group.

Table 1: Characteristics of the studies selected for meta-analysis Articles selected include 28 data sets representing 5236 subjects. Ethnic origin of subjects identified as follows: Country (either Asian (A) or Non-Asian (Non-A); Mixed (includes samples includes Canada, Finland, Sweden, Norway, Israel, Spain)

Authors	Ref.	Sex (Male /Female)	Age (years) mean SD)	Year	County of origin (Ethnic origin)	Sample size	BMI Kg/m² Mean (SD)	FPG mmol/L) Mean (SD)	TC (mmol/L) Mean (SD)	HDL (mmol/L) Mean (SD)	LDL (mmol/L) Mean (SD)	TG (mmol/L) Mean (SD)
Ek 1 *et al*.	**[36]**	93/105	52(14)	2001	Denmark (Non-A)	198	25.23(3.86)	5.1(0.44)	5.47(1.10)	1.43(0.40)	NA	1.18(0.68)
Ek 2 *et al*.	**[36]**	134/159	61(1)	2001	Denmark (Non-A)	293	26.15(3.68)	5.15(0.50)	6.25(0.99)	1.49(0.44)	NA	1.34(0.78)
Andrulionyte *et al.*	**[26]**	387/383	55(8)	2004	Mixed population	770	30.76(3.98)	6.26(0.53)	5.67(1.01)	1.19(0.32)	3.60(0.90)	2.00(1.10)
Ambye *et al*.	**[17]**	1108/1147	NA	2005	Denmark (Non-A)	2255	25.83(4.14)	4.79(0.50)	6.14(1.10)	1.41(0.40)	4.04(1.00)	1.40(0.99)
Vohl 1 *et al*.	**[31]**	NA	40(10)	2005	Canada (Non-A)	173	53.14(10.08)	5.48(0.80)	5.04(0.94)	1.20(0.32)	3.00(0.81)	1.86(0.95)
Vohl 2 *et al*.	**[31]**	NA	48(9)	2005	Canada (Non-A)	84	52.21(9.96)	8.06(2.84)	4.76(0.97)	1.14(0.33)	2.63(0.87)	2.30(1.19)
Hui 1 *et al*.	**[37]**	NA	51(11)	2008	China (A)	96	24.81(1.99)	5.43(1.14)	5.69(2.62)	2.00(0.89)	3.60(0.65)	3.49(1.69)
Hui 2 *et al*.	**[37]**	NA	51(11)	2008	China (A)	96	24.37(2.09)	4.93(0.64)	5.83(1.17)	2.13(1.06)	3.27(0.68)	2.13(1.54)
Zhang 1 *et al*.	**[27]**	NA	62(5)	2007	China (A)	282	23.62(3.19)	NA	4.57(1.59)	1.58(0.42)	2.29(1.45)	1.62(1.08)
Zhang 2 *et al*.	**[27]**	NA	64(6)	2007	China (A)	263	24.10(2.54)	NA	5.34(1.48)	1.50(0.35)	2.99(1.16)	1.84(1.44)
Goyenechea *et al.*	**[28]**	93/87	35(6)	2008	Spain (Non-A)	180	31.20(3.06)	5.06(0.41)	5.32(0.94)	1.36(0.340	3.43(0.82)	NA
Okauchi *et al.*	**[32]**	74/81	62(10)	2008	Japan (A)	155	24.91(5.39)	9.17(2.63)	5.29(1.07)	1.25(0.34)	NA	1.64(0.91)
Chae 1 *et al*.	**[38]**	NA	26(6)	2010	South Korea (A)	184	22.15(4.83)	4.90(0.89)	4.53(1.20)	1.55(0.43)	NA	1.23(0.73)
Chae 2 *et al*.	**[38]**	NA	29(4)	2010	South Korea (A)	256	20.25(2.89)	4.95(0.45)	4.37(0.68)	1.65(0.33)	NA	0.78(0.28)
Niktin 1 *et al*.	**[29]**	NA	56(9)	2010	Russia (Non-A)	132	29.25(6.48)	NA	4.87(0.92)	1.68(0.18)	2.84(0.25)	1.45(0.09)
Niktin 2 *et al*.	**[29]**	NA	59(8)	2010	Russia (Non-A)	313	28.38(5.14)	NA	5.58(0.97)	1.44(0.20)	3.75(0.36)	1.65(0.14)
Zhang *et al.*	**[27]**	125/116	49(10)	2010	China (A)	241	24.96(3.2)	8.92(3.47)	4.91(1.95)	1.33(0.70)	2.88(1.08)	3.00(3.33)
Geloneze *et al.*	**[39]**	47/8	37(10)	2012	Brazil (NA)	55	44.47(5.52)	5.15(1.21)	4.50(0.85)	1.11(0.28)	2.84(0.66)	1.48(0.37)
Miraezi *et al*.	**[24]**	NA	37(12)	2012	Iran (Non-A)	229	30.25(6.54)	5.69(1.86)	4.42(0.79)	1.15(0.27)	2.47(0.59)	1.37(0.63)
Nishida *et al.*	**[40]**	Males only	47(5)	2015	Japan (A)	112	25.65(2.39)	5.55(0.59)	5.50(0.79)	1.29(0.29)	3.43(0.70)	1.76(1.31)

Shokouhi 1 *et al*.	**[41]**	82/91	53(10)	2015	Iran (Non-A)	173	26.91(4.35)	NA	4.63(1.09)	3.01(0.70)	3.04(0.80)	1.65(0.46)
Shokouhi 2 *et al*.	**[41]**	73/100	55(11)	2015	Iran (Non-A)	173	28.81(4.88)	NA	5.13(1.07)	0.93(0.24)	3.41(0.94)	2.07(0.47)
Vazques-Delmercado 1 *et al*.	**[14]**	NA	38(14)	2015	Mexico (Non-A)	153	22.45(1.66)	4.83(0.62)	4.45(0.96)	1.03(0.43)	2.73(0.93)	1.30(0.73)
Vazques-Delmercado 2 *et al*.	**[14]**	NA	38(14)	2015	Mexico (NA)	144	27.39(1.43)	5.31(0.68)	4.96(1.05)	0.93(0.34)	2.92(0.94)	1.89(1.17)
Vazques-Delmercado 3 *et al*.	**[14]**	NA	38(14)	2015	Mexico (Non-A)	78	34.15(3.27)	5.38(0.75)	4.96(0.81)	0.97(0.37)	3.02(0.69)	1.72(0.90)
Tai *et al*.	**[42]**	56/62	30(10)	2016	Taiwan (A)	177	41.88(7.56)	5.85(1.74)	5.09(1.01)	1.21(0.28)	3.41(0.94)	1.69(1.16)
Tobina *et al*.	**[43]**	49/70	71(7)	2016	Japan (A)	119	23.81(3.25)	NA	5.46(0.79)	1.56(0.37)	3.34(0.74)	1.21(0.7)
Ramos-Lopez *et al.*	**[44]**	NA	NA	2018	Spain (Non-A)	107	31.75(3.65)	5.30(0.64)	5.61(0.94)	1.36 (0.32)	3.54 (0.81)	NA

No differences were evident for any of the components of the lipid profile (TC, HDL, LDL, TG) when the total population was analysed ($p>0.05$ see table 2). However, when the studies were grouped based on participants representing an Asian or a non-Asian population a significant effect was observed in the total cholesterol level for the non-Asian group ($p<0.05$) with lower levels of TC for participants with AA genotype in comparison to combined "GG+GA" genotypes using a recessive genetic model (WMD = -0.11, 95% CI = -0.21 to -0.02) (Table 2, Figure 2a). No significant difference in TC levels was observed in "AA" genotype in comparison to "GG+GA" genotype group in Asian populations (WMD = 0.00, 95% CI = -0.11 to 0.12.

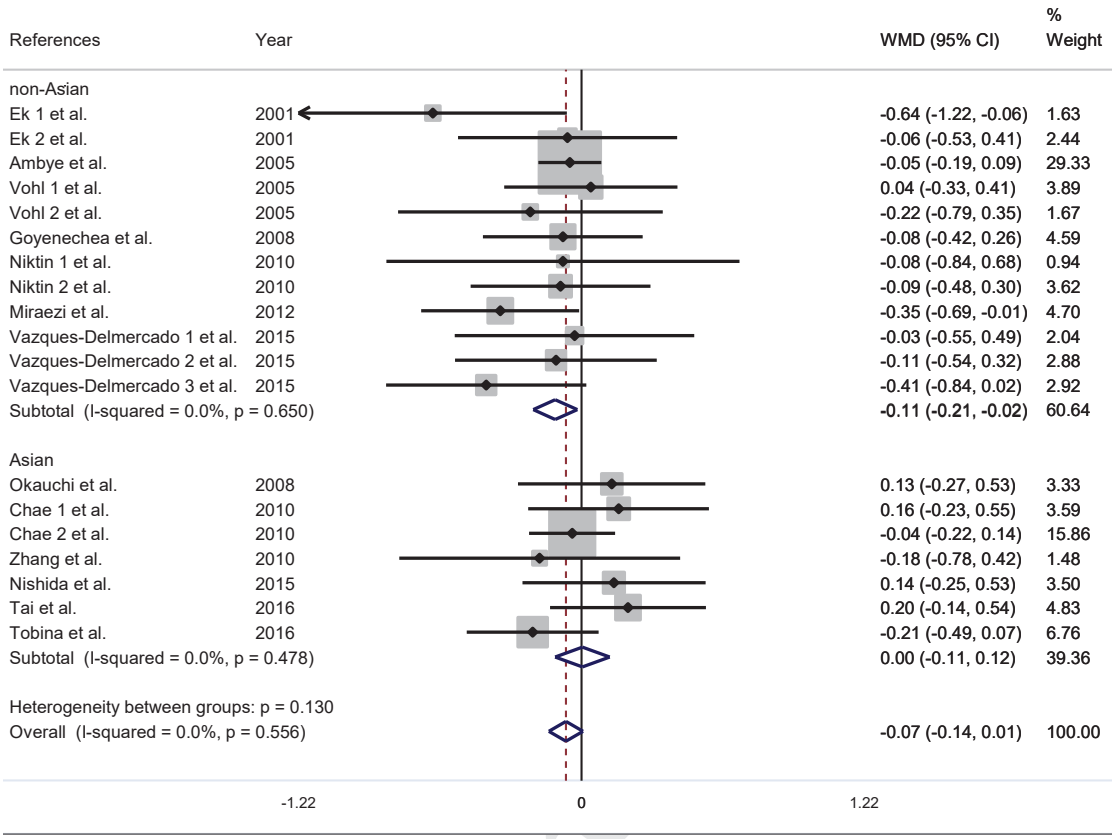


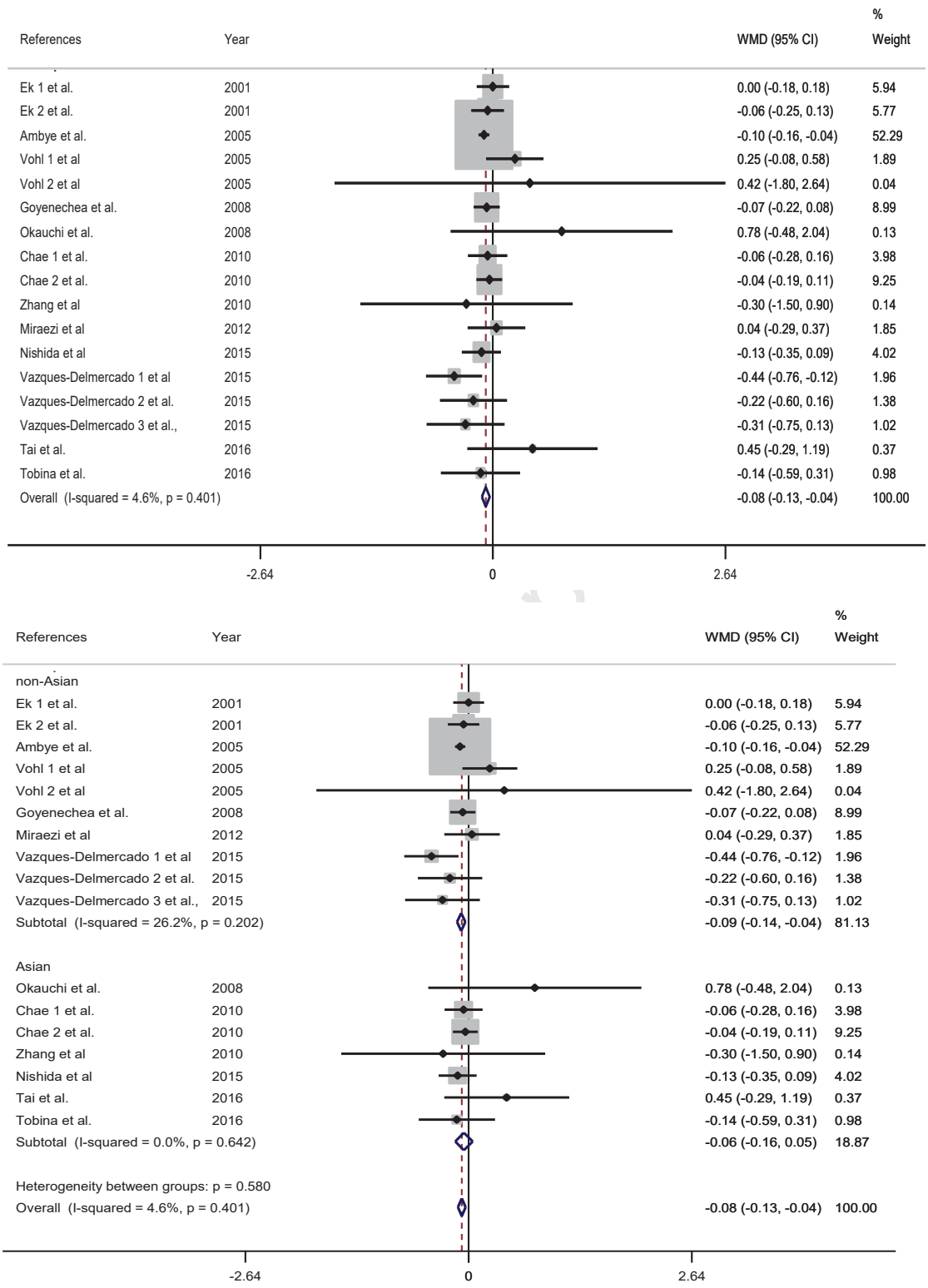
Figure 2. Forest plot showing graphical representation of studies identified from meta-analysis of Gly482Ser variant of PPARGC1A of total cholesterol (TC) levels under the recessive genetic model using fixed effect model with a comparison with Non- Asian and Asian groups. At the bottom of the Forest plot the scale used to accommodate the range of confidence interval is included e.g. -1.22 - +1.22.

Table 2: Summary of meta-analysis of Gly482Ser variant of PPARGC1A with lipid profile fasting blood glucose and body mass index

Test	Genetic models[†]	Heterogeneity	Statistical model[ǂ]	Total population WMD[§]	Total population p-value	Asian WMD	Asian p-value	Non-Asian WMD	Non-Asian p-value
HDL	D (GG vs. GA+AA)	Yes	Rn	-0.02	0.13	-0.01	0.16	-0.03	0.37
	R (AA vs. GG+GA)	Yes	Rn	-0.02	0.38	-0.03	0.90	0.00	0.33
LDL	D (GG vs. GA+AA)	Yes	Rn	0.01	0.89	-0.03	0.63	0.03	0.67
	R (AA vs. GG+GA)	No	F	-0.05	0.11	-0.09	0.26	-0.04	0.20
TG	D (GG vs. GA+AA)	Yes	Rn	0.01	0.74	0.04	0.26	0.00	0.92
	R (AA vs. GG+GA)	No	F	-0.02	0.35	-0.02	0.65	-0.02	0.41
TC	D (GG vs. GA+AA)	Yes	Rn	0.05	0.32	-0.01	0.92	0.08	0.15
	R (AA vs. GG+GA)	No	F	-0.07	0.07	0.00	0.95	-0.11	**≤0.05**
FPG	D (GG versus GA+AA)	Yes	Rn	-0.01	0.69	-0.03	0.64	-0.01	0.84
	R (AA versus GG+GA)	No	F	-0.08	**≤0.001**	-0.06	0.14	-0.09	**≤0.001**
BMI	D (GG versus GA+AA)	No	F	0.13	0.1	0.32	**≤0.05**	0.04	0.68
	R (AA versus GG+GA)	No	F	-0.08	0.54	-0.08	0.12	0.08	0.65

[†] D= dominant model R = Recessive model; No = heterogeneity statistically significant; Yes = heterogeneity statistically not significant.[ǂ] Rn = random, F = fixed; ;
[§] WMD = weighted mean difference. BMI = body mass index; HDL = high-density lipoprotein; LDL= low-density lipoprotein; TG = triglyceride; TC = total cholesterol; FPG = Fasting plasma glucose. Results at less than 5% statistically significance level (i.e. <0.05) are presented in bold text

In the total group the FPG data demonstrated that there was an association with genotype ($p<0.001$) (Table 2 Fig 3) with a significantly reduced FPG level in AA genotypes in comparison with GG+GA genotypes indicating a protective effect of the minor allele ($p\leq0.001$) (Table 2; Fig 3a). This was also evident in the non-Asian group ($p\leq0.001$) (WMD = -0.08, CI: - 0.13 to -0.03) (Table 2, Fig. 3b), while for the Asian population there was no support for a protective effect from the minor allele (Table 2, Fig. 3b).



b)

Figure 3. Forest plot showing graphical representation of studies identified from meta-analysis of Gly482Ser variant of PPARGC1A fasting plasma glucose (FPG) identified from meta-analysis using the fixed effect model under recessive model with the total population (a) and with the Asian and non-Asian subgroups (b). At the bottom of the Forest plot the scale used to accommodate the range of confidence interval is included e.g. -2.64 – +2.64.

Total population studies demonstrated that there was no association with BMI and genotype (p=0.1 and p=0.54 under the dominant and the recessive model respectively) (Table 2). However, the dominant model data generated from the Asian studies demonstrated a significantly higher BMI for "GG" genotype in comparison to "GA+AA" genotype group under the dominant genetic model (WMD = 0.32, CI: 0.04 to 0.60, p- <0.05 (Table 2), but this was not evident within the non-Asian studies (p=0.68) (Table 2). No significant heterogeneity was observed in either the non-Asian (I^2 = 0%, p = 0.93) or the Asian populations with respect to BMI (I^2 = 0 %, p = 0.66) (Fig. 4). BMI for the Asian group was found to be significantly

The protection conferred by the minor allele for a lower BMI is particularly relevant to the Asian population given the ethnic-specific criteria for the diagnosis of metabolic syndrome [1]; namely a reduced waist circumference is advised for the Asian population for diagnosis of metabolic syndrome and a lower BMI advised as a risk factor for the Asian population.

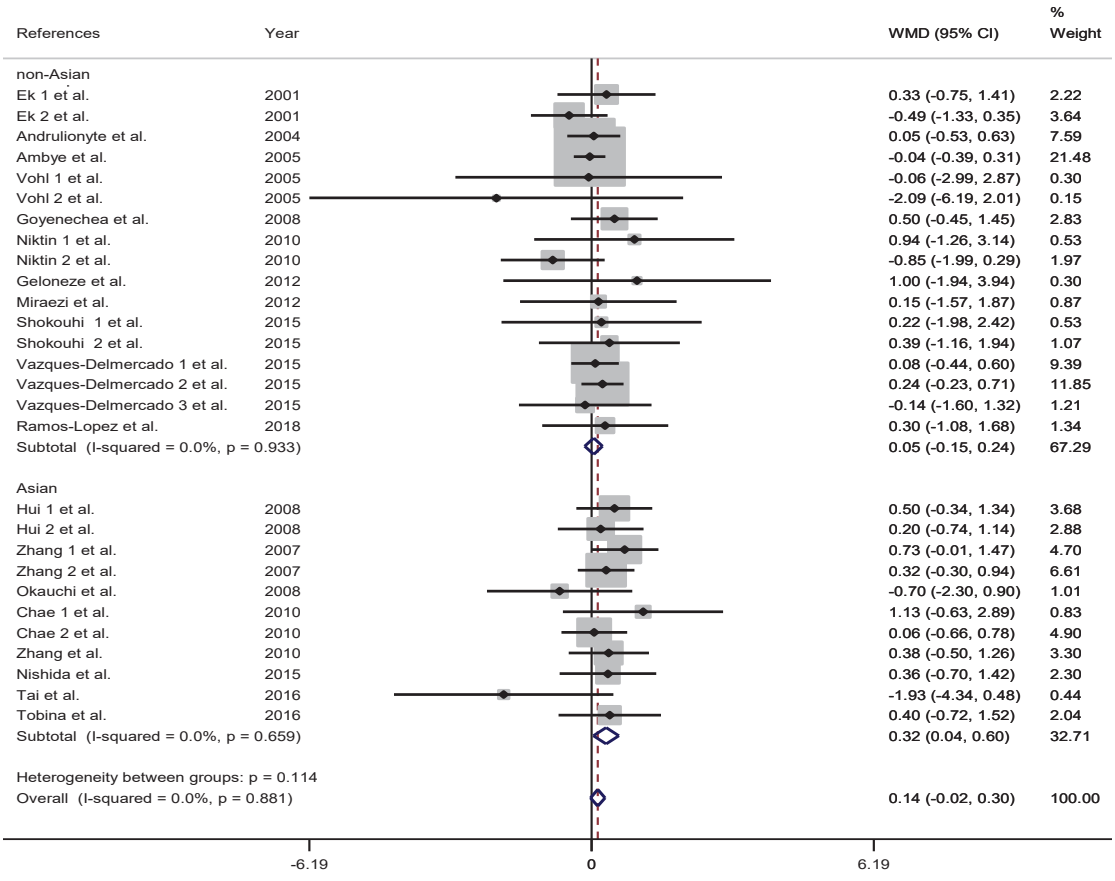


Figure 4. Forest plot illustrating body mass index levels (BMI) identified from meta-analysis of Gly482Ser variant of PPARGC1A using the fixed effect model under the dominant genetic model with a comparison of Non- Asian and Asian groups. At the bottom of the Forest plot the scale used to accommodate the range of confidence interval is included e.g. -6.19 - +6.19.

4.0 Discussion

The present study has shown that the Gly482Ser variant of PPARGC1A gene is significantly associated with BMI in Asian populations under the dominant genetic model. Furthermore, the SNP is significantly associated with total cholesterol in non-Asians under the recessive genetic model and was significantly associated with fasting plasma glucose in the total population (including Asian and Non-Asian) and in the non-Asian population.

Many emerging lines of evidence suggest an important role of PPARGC1A in lipid metabolism [4, 5, 45, 46, 47] especially in skeletal muscle [6] and liver [3]. PPARGC1A Gly482Ser is one of the most studied variants and some recent studies indicated its association with lipid levels [14, 23, 43,]. To our knowledge, this is the first time a meta-analysis of the association of this SNP with lipid profile has been conducted. Other components of metabolic syndrome in humans have been included to address conflicting results from the literature.

In this study, using the dominant genetic model, the BMI of those individuals with the GG genotype is significantly higher in Asian subgroups. Taken individually the articles including the Asian data in the meta-analysis do not show any significant difference under either the dominant or recessive model but the power has been improved by combining data in the meta-analysis. In contrast, reports have indicated that the minor allele being associated with type 2 diabetes susceptibility [36], relative risk of obesity [47] insulin resistance [26] and reduced beta cell function [48 kleiner]. The association of this SNP with BMI in the Tongan population is evident where BMI was elevated under both a co-dominant and a dominant model [49]. The Tongan population have the Gly482Ser variant present at high frequency and may have been conserved within the population as a thrifty gene. However, it is clear that generalisations cannot be made as the minor allele of this SNP is associated with elevated body mass in Korean children [13] and non-diabetic overweight Chinese subjects [15].

There are clearly a number of different variables that are important for the Gly482Ser genotype to contribute to the BMI profile. The power of the present study with respect to BMI could have been improved as we excluded a number of articles with relevant BMI data as they did not include lipid levels as this was the prime focus of the study. However, it does highlight an interesting difference between the Asian and the non-Asian populations that is also reflected in the

differential diagnosis of metabolic syndrome with a lower BMI cut off point for individuals of Asian origin [1].

The reduction of fasting plasma glucose levels in AA genotypes also has differential significance with the two population groups. The analysis of the overall population and the non-Asian group indicated that the minor allele had a protective effect against elevated fasting glucose in the non-Asian population but this was not evident in the Asian group. Furthermore, the total cholesterol level was reduced in the non-Asian group with a similar protective effect of the homozygous recessive genotype. The apparent protective effect of the minor allele (Ser) in the non-Asian study group is supported by studies that propose that the presence of the major allele (Gly) has been associated with reduced cardiorespiratory fitness in Japanese men [40].

These studies have been conducted in different population groups that are defined by the primary aim of the respective studies such as type 2 diabetes, CAD (coronary artery disease), morbidly obese, obese, pre-obese, NAFLD (Non-alcoholic fatty liver disease) and the elderly age group. This could exacerbate the heterogeneity and thus confound the distinction between the Asian and non-Asian group. While the heterogeneity of the population group may contribute to the study outcome, it is also evident that the ubiquitous nature of PPARGC1A in such fundamental processes as energy metabolism, lipid regulation, oxygen uptake, adipogenesis and insulin signalling presents a highly complex system that may also be a source of heterogeneity. Thus, specific follow up of outcomes demonstrating differential effects between non-Asian and Asian population and the apparent protective effect of the minor allele in the Asian group warrants further scrutiny. Epigenetic changes may contribute to this dichotomy [50, 51] and may explain the variation seen in distinct ethnic population groups as evident in the outcomes from the present study.

Conflict of Interest

All authors have no conflicts of interest to disclose.

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Contributors

All authors contributed to the writing of the manuscript. PB conducted the study as part of his PhD study and the remaining authors were members of his supervisory team.

Supplementary Table 1: Components of metabolic syndrome as defined from the National Cholesterol Education Programme, Adult Treatment Panel III, EGSIR (NCEP ATP III modified) [1] M (male); F (female)

Impaired fasting glucose	≥ 5.6 mmol/L or diagnosed with diabetes.
Waist circumference	European ≥94 cm (M) or ≥80cm (F), United States ≥ 102 (M) or ≥88 (F), South Asian ≥90 cm (M) or ≥80cm (F), Chinese ≥85 cm (M) or ≥80cm (F), Japanese ≥85 cm (M)or ≥90 cm (F)
Blood pressure	≥130/85mmHg or medication
Triglycerides	s≥1.7mmol/l or medication,
Cholesterol	HDL-C <1.0mmol/l (M) and <1.30mmol/l (F) or on medication

Supplementary Table 2: Search term used for systematic review of Peroxisome proliferator activator receptor type 1 alpha and the Gly482Ser polymorphism

Data base	**Terms used**	**Number of articles identified**
Web of Science	("Peroxisome proliferator activator receptor gamma coactivator 1" or PPARGC1A or PGC-1 or PGC-1alpha or PGC1alpha) AND (Polymorphism or Gly482Ser or "rs8192678")	**291**
Pub med	("Peroxisome proliferator activator receptor gamma coactivator 1" or "PPARGC1A" or "PGC-1" or "PGC-1alpha" or "PGC1alpha") and "polymorphism" or "Gly482Ser" or "rs8192678"	**241**
Embase	("Peroxisome proliferator activator receptor gamma coactivator 1" or "PPARGC1A" or "PGC-1" or "PGC-1alpha" or "PGC1alpha") and "polymorphism" or "Gly482Ser" or "rs8192678"	**309**
Cochrane	("Peroxisome proliferator activator receptor gamma coactivator 1" or "PPARGC1A" or "PGC-1" or "PGC-1alpha" or "PGC1alpha") and "polymorphism" or "Gly482Ser" or "rs8192678"	**9**
	total	**850**

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Meta-analysis demonstrates Gly482Ser variant of PPARGC1A is associated with components of metabolic syndrome within Asian populations

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HIGHLIGHTS:

- This is the first meta-analysis where cholesterol has been used as an indicative element in the data search strategy for this variant;
- The work demonstrates a genetic distinction at the level of the BMI between the Asian and non-Asian population groups (important criteria in the management of metabolic syndrome and diabetes);
- the AA genotype group showed significantly lower levels of total cholesterol (TC) compared to GG+GA genotype using the recessive model in the non-Asian population group that was not evident in the Asian sample.