VDR Gene variation and insulin resistance related diseases

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Abstract

Background: Vitamin D status may influence the risk of insulin resistance related diseases such as Type 2 diabetes (T2DM), metabolic syndrome (MetS), and polycystic ovarian syndrome (PCOS). Several studies have assessed vitamin D receptor (VDR) gene polymorphism in relationship with these diseases; however, results remain inconsistent. Our study was conducted to elucidate whether VDR Gene polymorphisms could predict insulin resistance on a large scale.

Methods: A meta-analysis using MEDLINE and EMBASE, was performed up to December 16th, 2016. Studies reporting association of vitamin D gene polymorphism with incident T2DM, MetS and PCOS outcomes were included and sub-group analysis by pigmentation of skin and latitude were performed.

Results: A total of 28 articles based on four gene variation, and comprising 9232 participants with 5193 insulin resistance related diseases patients were included. No significant associations of the VDR ApaI, BsmI, FokI and TaqI variant with insulin resistance related diseases were found. However, sub-group analysis analysis showed that PCOS in TaqI (OR = 1.47, 95% CI = 1.03–2.09, \( P = 0.03 \)) for T allele and MetS for G allele (OR = 1.41, 95% CI = 1.07–1.85, \( P = 0.01 \)) in BsmI was significant association with VDR gene polymorphism. Simultaneously, sub-group analysis showed VDR ApaI rs7975232(G > T) variant was associated with insulin resistance related diseases in Asians (GG/GT + TT) (OR, 1.62; 95% CI, 1.03–2.53; \( P = 0.04 \)) and population who lived in middle latitude district (30–60°) (GG/GT + TT) (OR, 1.22; 95% CI, 1.04–1.43; \( P = 0.02 \)), VDR BsmI rs1544410 (A > G) and VDR Taq1rs731236 (T/C) variant were associated with insulin resistance related diseases in Caucasian (dark-pigmented).

Conclusion: The results suggested that the association between insulin resistance related diseases and VDR ApaI, BsmI, FokI variant was more obvious in dark-pigmented Caucasians and Asians but not in Caucasian with white skin.

Keywords: VDR Gene polymorphisms, Type 2 diabetes (T2DM), Metabolic syndrome (MetS), Polycystic ovarian syndrome (PCOS)

Background

Vitamin D deficiency as a common health problem is a global problem, thought to be related to lack of sunlight exposure, and usually accompanied by reduced dietary intake [1]. The Vitamin-D receptor (VDR) was studied as a genetic factor of spine pathologies and plays a part in normal bone mineralization and remodeling. It is an endocrine member belongs to the nuclear receptor superfamily for steroid hormones. Its gene polymorphisms are thought to contribute to osteoarthritis, osteoporosis and degenerative disc disease. Also researchers found that VDR regulates vitamin D levels and calcium metabolism in the body and these are known to be associated with endocrine dysfunctions, insulin resistance [2, 3]. Vitamin D has been reported to influence glucose regulation via effects on insulin secretion and action [4]. Evidence is accumulating to suggest that altered vitamin D and Ca homeostasis may play a role in the development of metabolic disturbances in insulin resistance related diseases [5–7]. More and more studies found that the vitamin D was useful for insulin resistance diseases [8–10].

T2DM, MetS, and IFG are common metabolic disorders which are observed with increasing prevalence, and which are caused by a complex interplay between genetic and environmental factors, and these metabolic disorders are all
characterized by insulin resistance [11–13]. PCOS is by far the most common cause of anovulatory infertility and has been reported to be associated with insulin resistance (IR), hyperinsulinemia, dyslipidemia, and central obesity, which are all risk factors for the MetS, T2DM, and cardiovascular disease. Several studies have assessed vitamin D receptor gene polymorphism in relationship with these diseases; however, results remain inconsistent.

Vitamin D condition depends mainly on the sunlight and skin. It is both an environmental and biological determinant of health. Skin pigmentation may predispose subpopulations to vitamin D deficiency [14]. Some studies demonstrate that vitamin D deficiency is much higher in dark-pigmented population and Asians due to a reduced ability to produce vitamin D in their skin [15, 16]. Wondering whether there was any correlation or diverseness among these different population and their living latitude, in this research we also performed sub-group studies by skin pigmentation and latitude. Our study was conducted to elucidate whether VDR Gene polymorphisms could predict insulin resistance on a large scale.

Methods

Search strategy and selection criteria

Two investigators (Fei-fei Han, Ya-li Lv) independently searched PubMed and Embase (from 1980 until December 16th, 2016) database using the terms ((Gene polymorphism or gene variation)) AND (((((((diabetes mellitus) OR Diabetes) OR insulin resistance) OR metabolic syndrome) OR polycystic ovarian syndrome)) AND (vitamin D receptor OR VDR)).

Furthermore, we reviewed citations in the retrieved articles to search for additional relevant studies. Articles included in meta-analysis were in English or Chinese, with human subjects, published in primary literature and with no obvious overlap of subjects with other studies. The retrieved literatures were then read in their entirety to assess their appropriateness for the inclusion in this meta-analysis. Conference abstracts, case reports, editorials, review articles, and letters were excluded. We defined strict criteria for inclusion of studies. Studies were included if the exposure of interest was the VDR genotype.

Data extraction

Two independent authors extracted data and reached a consensus on the author, year of publication, ethnicity, number of patients and controls and disease types.

Statistical analysis

All statistical analyses were performed using Review Manager (Review Manager 5.0 software) and Stata/MP 11.0. Cochran’s w² test and the inconsistency index (I²) were used to evaluate heterogeneity across the included studies. Random-effects model was applied in all the analysis. OR and their corresponding 95% confidence intervals (CI) were estimated. Z-test was performed to determine the statistical significance of pooled OR, and was considered significant when \( P < 0.05 \). We assessed potential publication bias by using a funnel plot and Egger’s test. Sensitivity analysis was performed by sequential removal (statistics of study remove) of individual studies (we did not show these results) [17].

Results

Eligible studies for meta-analysis

This study is focusing on VDR Apal rs7975232 (G > T) variant, BsmI rs1544410 (A > G) variant, Taq1rs731236 (T > C) variant and FokIrs2228570 (C > T) variant and Insulin resistance related diseases susceptibility including (T2DM, MetS and PCOS). Characteristics of studies investigating the association of the variants with Insulin resistance related diseases susceptibility are presented in Table 1. The research of the VDR variant identified 54 articles. However, 26 studies were excluded for no case-control or no data. Finally, 28 studies were included in the current meta-analysis (Fig. 1).

Of these, 14 case-control studies examined the association of the Apal rs7975232 (G > T) variant [3, 18–30] (Table 1), 22 studies in 20 case-control papers examined the association of the BsmI rs1544410 (A > G) variant [18, 22, 23, 27–39] (Table 2), 19 studies in 18 case-control studies examined the association of the Taq1rs731236 (T > C) variant [3, 18–28, 32, 33, 35, 38–40] (Table 3) and 18 studies in 16 case-control studies in15 papers examined the association of FokIrs2228570 (C > T) variant [3, 18, 23–25, 27, 30–32, 36, 41–45] (Table 4) with Insulin resistance related diseases susceptibility.

Association between VDR Apal rs7975232 (G > T) variant and insulin resistance related diseases susceptibility

Fourteen studies (3212 cases and 3360 controls) examining the association between the VDR Apal rs7975232 (G > T) variant and Insulin resistance related diseases susceptibility were included. Sub-group analysis (nine studies about T2DM and five studies about PCOS) was performed. All the original data were combined by means of the Random effect model. We found no association of the VDR Apal rs7975232 (G > T) variant with Insulin resistance related diseases (OR, 1.08; 95% CI, 0.91–1.28; \( P = 0.37 \)) in the recessive genetic model (G/G vs.G/T or T/T), dominant genetic model in the (G/G or G/T vs.T/T) (OR, 1.04; 95% CI, 0.89–1.21; \( P = 0.62 \)) and G allele vs. T allele analysis (OR, 1.04; 95% CI, 0.95–1.1; \( P = 0.36 \)). sub-group analysis indicated that there was no association between VDR Apal rs7975232 (G > T) variant and T2DM, PCOS patients (Table 5). sub-group analysis by skin pigmentation and living latitude showed that Apal rs7975232 (G > T) variant
was associated with insulin resistance related diseases in Asians (GG/GT + TT) (OR, 1.62; 95% CI, 1.03–2.53; \( P = 0.04 \)) and population who lived in middle latitude district (30°–60°) (GG/GT + TT) (OR, 1.22; 95% CI, 1.04–1.43; \( P = 0.02 \)). No publication bias was detected by either the funnel plot or Egger’s tests (\( P > 0.05 \), each comparison).

### Association between VDR BsmI rs1544410 (A > G) variant and insulin resistance related diseases susceptibility

Twenty-two studies (4294 cases and 4157 controls) in 17 papers examining the association between the VDR BsmI rs1544410 (A > G) variant and Insulin resistance related diseases susceptibility were included. Sub-group analysis (14 studies about T2DM, four studies about PCOS and four studies about Mets) was performed. All the original data were combined by means of the Random effect model. We found no association of the VDR BsmI rs1544410 (A > G) variant with Insulin resistance related diseases (OR, 0.95; 95% CI, 0.78–1.16; \( P = 0.64 \)) in the recessive genetic model (A/A vs. A/G or G/G), dominant genetic model in the (A/A or A/G vs. G/G) (OR, 1.06; 95% CI, 0.86–1.31; \( P = 0.59 \)) and A allele vs. G allele analysis (OR, 0.97; 95% CI, 0.83–1.13; \( P = 0.67 \)).

### Table 1 Characteristics of studies on VDR ApaI rs7975232 (G > T) variant and Insulin resistance related diseases susceptibility

| Author        | Year | Country       | Ethnicity          | City latitude  | Disease | Case | Control |
|---------------|------|---------------|--------------------|----------------|---------|------|---------|
| Al-Daghri NM  | 2012 | Saudi         | Caucasian (dark)   | Riyadh 24°38’N | T2DM    | 148  | 172     |
| Boullu-Sanchis, S | 1999 | France (migrant Indian population) | Caucasian (Dark) | Guadeloupe 16°15’N | T2DM     | 22   | 42      |
| Dasgupta S    | 2015 | India         | Caucasian (Dark)   | Hyderabad 17°23’N | PCOS    | 117  | 120     |
| Dilmec F      | 2008 | India         | Caucasian (Dark)   | Sanliurfa 37°17’N | T2DM    | 27   | 38      |
| El-Shal AS    | 2013 | Egypt         | Caucasian (Dark)   | Zagazig 30°35’N  | PCOS    | 63   | 65      |
| Oh, J. Y.     | 2001 | USA           | Caucasian          | Southern California 32°42’N | T2DM | 84   | 92      |
| Jedrzejuk D   | 2015 | Poland        | Caucasian          | Wroclaw 51°1’N   | PCOS    | 19   | 52      |
| Mahmoudi T    | 2009 | Iran          | Caucasian (Dark)   | Tehran 35°40’N   | PCOS    | 58   | 68      |
| Malecki MT    | 2003 | Poland        | Caucasian          | Krakow 50°08’N   | T2DM    | 71   | 153     |
| Rivera-Leon EA | 2015 | Mexico        | Mix                | Western of Mexico (Guadalajara 20°67’N) | T2DM | 47   | 64      |
| Wehr E        | 2011 | Austria       | Caucasian          | Graz 47°4’N      | PCOS    | 142  | 274     |
| Ye WZ         | 2001 | France        | Caucasian          | Paris 48°52’N    | T2DM    | 98   | 142     |
| Zhong X       | 2015 | China         | Asian              | Anhui Province 31°52’N | T2DM | 29   | 114     |
| Zhang H       | 2012 | China         | Asian              | Changsha 28°12’N | T2DM    | 30   | 154     |

**Fig. 1** Flow diagram for study selection in meta-analysis
group analysis indicated that there was no association between BsmI rs1544410 (A > G) variant and T2DM, PCOS patients. However, significant association was found in MetS sub-group analysis G allele vs. A allele analysis (OR, 1.41; 95% CI, 1.07–1.85; \( P = 0.01 \)) (Table 5). sub-group analysis by skin pigmentation and living latitude showed that VDR BsmI rs1544410 (A > G) variant was associated with insulin resistance related diseases in Caucasian (dark-pigmented) (AA + GA/GG) (OR, 1.50; 95% CI, 1.16–1.93; \( P = 0.002 \)), (A allele) (OR, 1.23; 95% CI, 1.07–1.42; \( P = 0.004 \)). No publication bias was detected by either the funnel plot or Egger’s tests (\( P > 0.05 \), each comparison).

**Association between VDR TaqI rs731236 (T/C) variant and insulin resistance related diseases susceptibility**

Nineteen studies (3533 cases and 4024 controls) examining the association between the VDR Taq1rs731236 (T/C) variant and Insulin resistance related diseases susceptibility were included. Sub-group analysis (13 studies about T2DM, six studies about PCOS) was performed. All the original data were combined by means of the Random effect model. We found no association of the VDR Taq1 rs731236 (T/C) variant with Insulin resistance related diseases (OR, 1.00; 95% CI, 0.82–1.21; \( P = 0.96 \)) in the recessive genetic model (T/T vs. T/C), dominant genetic model in the (T/T or T/C vs. C/C) (OR, 0.88; 95% CI, 0.73–1.06; \( P = 0.17 \)), T allele (OR, 0.89; 95% CI, 0.75–1.06; \( P = 0.18 \)). Sub-group analysis indicated significant association between VDR Taq1rs731236 C allele and PCOS in C allele analysis (OR1.47; CI 1.03–2.09; \( P = 0.03 \)) (Table 5). sub-group analysis by skin pigmentation and living latitude showed that VDR TaqI rs731236 (T/C) variant was associated with insulin resistance related diseases in Caucasian (dark-pigmented) (C allele) (OR, 1.24; 95% CI, 1.05–1.47; \( P = 0.01 \)). No publication bias was detected by either the funnel plot or Egger’s tests (\( P > 0.05 \), each comparison).

**Association between VDR FokI rs2228570 (C > T) variant and insulin resistance related diseases susceptibility**

Eighteen studies (4851 cases and 6174 controls) from 17 papers examining the association between the VDR FokIrs2228570 (C > T) variant and Insulin resistance related diseases susceptibility were included. Sub-group
and CaMKs stimulates VDR-Mediated transcription by genes such as Calmodulin-Dependent Kinase (CaMKs), D3 by controlling the expression of hormone sensitive transcription factor that mediates the action of vitamin VDR, which is considered as a pleiotropic gene, is a discussion.

**Table 3** Characteristics of studies on VDR Taq1rs731236 (T/C) variant and Insulin resistance related diseases susceptibility

| Author                  | Year | Ethnic     | Ethnic City latitude | Disease     | Case   | Control |
|-------------------------|------|------------|----------------------|-------------|--------|---------|
| Al-Daghri NM [18]       | 2012 | Saudi      | Riyadh 24°38’N       | T2DM        | 65     | 195     |
| Bagheri M [40]          | 2013 | Iran       | Urmia 37°33’N        | PCOS        | 8      | 14      |
| Bid HK [32]             | 2009 | Indian     | North Indian         | T2DM        | 15     | 49      |
| Boullu-Sanchis, S [19]  | 1999 | France     | Guadeloupe 16°15’N   | T2DM        | 48     | 33      |
| Dasgupta S [48]         | 2015 | India      | Hyderabad 17°23’N    | PCOS        | 47     | 92      |
| Dilmec F [21]           | 2008 | Turkey     | Sanliurfa 37°17’N    | T2DM        | 14     | 25      |
| El-Shal AS [20]         | 2013 | Egypt      | Zagazig 30°35’N      | PCOS        | 36     | 74      |
| Oh, J° Y° [22]          | 2002 | USA        | Southern California 32°42’N | T2DM | 41     | 108     |
| Jedrzejuk D [23]        | 2015 | Poland     | Wroclaw 51°1’N       | PCOS        | 8      | 45      |
| Mahmoudi T [24]         | 2009 | Iran       | Tehran 35°40’N       | PCOS        | 20     | 71      |
| Malecki MT [25]         | 2003 | Poland     | Krakow 50°08’N       | T2DM        | 71     | 153     |
| Mukhopadhyayna PN [33]  | 2010 | Indian     | Pune 18°52’N         | T2DM        | 5      | 12      |
| Rivera-Leon EA [49]     | 2015 | Mexico     | Mix western of Mexico | T2DM | 25     | 62      |
| Vural HC [35]           | 2012 | Turkey     | Konya 37°86’N        | T2DM        | 3      | 46      |
| Wehr E [27]             | 2011 | Austria    | Graz 47°4’N          | PCOS        | 72     | 238     |
| Xu, J. R. [39]          | 2014 | Chinese Han| Ningxia province 35–39’N | T2DM | 176    | 24      |
| Xu JR, [38]             | 2012 | China      | Ningxia province 35–39’N | T2DM | 182    | 19      |
| Ye WZ [28]              | 2001 | France     | Paris 48°52’N        | T2DM        | 49     | 136     |

analysis (nine studies about T2DM, five studies about PCOS, three studies about MetS and one study about IFG) was performed. All the original data were combined by means of the Random effect model. We found no association of the VDR FokIrs2228570 (C > T) variant with Insulin resistance related diseases (OR, 1.00; 95% CI, 0.68–1.47; P = 0.99) in the recessive genetic model (C/C vs. C/T or T/T), dominant genetic model in the ((C/C or C/T vs. T/T) (OR, 0.86; 95% CI, 0.67–1.09; P = 0.21) and C allele vs. T allele analysis (OR, 0.96; 95% CI, 0.84–1.10; P = 0.53). sub-group analysis indicated that there was no association between FokIrs2228570 (C > T) variant and T2DM, PCOS and MetS patients (Table 5). sub-group analysis by skin pigmentation and living latitude showed that there were no association between VDR Taq1rs731236 (T/C) variant and insulin resistance related diseases in ethics with different skin pigment and in different latitudes. No publication bias was detected by either the funnel plot or Egger’s tests (P > 0.05, each comparison).

**Discussion**

VDR, which is considered as a pleiotropic gene, is a transcription factor that mediates the action of vitamin D3 by controlling the expression of hormone sensitive genes such as Calmodulin-Dependent Kinase (CaMKs), and CaMKs stimulates VDR-Mediated transcription by phosphorylation levels of VDR [46]. Recent research found that deletion of macrophage VDR promotes insulin resistance and monocyte cholesterol transport to accelerate atherosclerosis in mice [47] which suggested that VDR dysfunction might result in insulin resistance. The association between VDR polymorphisms and insulin resistance related diseases including T2DM, PCOS and MetS has been extensively researched, but the results obtained so far are conflictive, and the role of VDR polymorphisms remains unclear. The reasons for this disparity may be small sample sizes, low statistical power, differences in ethnicities, extensive geographic variations, and interactions with other genetic or environmental factors. Therefore, in order to overcome the limitations of individual studies, we performed a meta-analysis. Meta-analysis increases statistical power and resolution by pooling the results of independent analyses. In this meta-analysis, we combined data from published case–control studies to evaluate the genetic associations of Taq1, BsmI, ApaI and FokI polymorphisms with these insulin resistance diseases.

To the best of our knowledge, this is the first meta-analysis which takes into account the interaction of individual VDR polymorphisms with insulin resistance diseases. This meta-analysis, which included a total of 28 articles, examined the associations among four studied polymorphisms in the VDR ApaI variant, VDR BsmI variant, VDR Taq1 variant and VDR FokI variant and
insulin resistance related diseases. The results indicated that VDR ApaI variant, VDR BsmI variant and VDR FokI variant were not conspicuous risk factors for insulin resistance related diseases. The result provided no evidence of the association between VDR variant and insulin resistance related diseases. Yet the results were different when the researches were grouping by skin pigment and living latitude. Sub-group analysis suggested that the association between insulin resistance related diseases and VDR ApaI, BsmI, FokI variant was obvious in dark-pigmented Caucasian population and Asians.

However, to make conclusive estimates, many factors should be considered. In complex diseases such as T2DM, complex interactions between genetic and environmental factors have differential effects on disease susceptibility. Further characterization of VDR, in addition to traditional and related risk factors may facilitate early identification of patients at high risk for T2DM, and then elucidate new approaches for prevention and treatment. However, several limitations of the meta-analysis should be addressed. First, lack of the original data of the reviewed studies limited our further evaluation of potential interactions, because the interactions between and even different polymorphic loci of the same gene may influence the risk. Second, our results were based on unadjusted published estimates, and hence, we were unable to adjust them by possible confounders, for example Vitamin D level, and diet did not take into consider. Third, the number of articles and cases taking in this research is relatively small. In order to provide a more precise estimation on the basis of adjustment for confounders, more well-designed studies should be taking into account. Additionally, current evidence from prospective studies on the association between vitamin D gene polymorphism and risk of insulin resistance related diseases was limited by the use of vitamin D gene polymorphism or a single measurement of 25(OH)D concentrations. A single baseline measure of dietary vitamin D may not be able to take into account the within-individual variations of vitamin D levels across seasons or geographical location, as evident in sub-group analysis. Studies are, therefore, needed with geographical location and dietary vitamin D levels to adjust for its variability while quantifying the associations.

Conclusion
In summary, this meta-analysis provided evidence of the association between VDR BsmI variant and MetS and supporting that VDR BsmI variant G allele might be a susceptibility marker of MetS. TaqI variant was associated with PCOS for C allele and supporting that VDR TaqI variant C allele might be a susceptibility marker of PCOS. No significant association was found in the rest gene polymorphisms and these diseases related with insulin resistance diseases. The relationship of VDR gene

| Author          | Year | Country | Ethnic          | City latitude       | Disease | Case TT | Case TC | Case CC | Control TT | Control TC | Control CC |
|-----------------|------|---------|-----------------|---------------------|---------|---------|---------|---------|------------|------------|------------|
| Al-Daghri NM    | 2012 | Saudi   | Caucasian (dark)| Riyadh 24°38’N     | T2DM    | 213     | 133     | 22      | 129        | 111        | 19         |
| Bagheri M       | 2012 | Iran    | Caucasian (dark)| Urmia 37°33’N      | PCOS    | 22      | 20      | 4       | 29         | 15         | 2          |
| Bid HK          | 2009 | India   | Caucasian (dark)| North Indian About 22–37°N | T2DM    | 2       | 60      | 38      | 1          | 79         | 80         |
| Dasgupta S      | 2015 | India   | Caucasian (dark)| Hyderabad 17°23’N  | PCOS    | 8       | 87      | 155     | 9          | 88         | 152        |
| Jia J           | 2015 | China   | Asian           | Nanjing 31°14’N    | T2DM    | 120     | 336     | 212     | 408        | 973        | 579        |
| Jedrzejuk D     | 2015 | Poland  | Caucasian       | Wroclaw 51°1’N    | PCOS    | 11      | 51      | 28      | 25         | 50         | 23         |
| Mahmoudi T      | 2009 | Iran    | Caucasian (dark)| Tehran 35°40’N     | PCOS    | 12      | 67      | 83      | 7          | 59         | 96         |
| Malecki MT      | 2003 | Poland  | Caucasian       | Krakow 50°08’N    | T2DM    | 64      | 159     | 85      | 52         | 110        | 77         |
| Mackawy A M     | 2014 | Egypt   | Caucasian (dark)| Zagazig 30°35’N    | T2DM    | 34      | 40      | 66      | 5          | 11         | 44         |
| Shah DB         | 2015 | India   | Caucasian (dark)| Telangana 17°49’N  | T2DM    | 15      | 9       | 10      | 11         | 10         | 2          |
| Schuch NJ       | 2013 | Brazil  | Mix             | São Paulo 23°33’N  | Mets    | 40      | 47      | 13      | 35         | 57         | 8          |
| Vedralová M     | 2012 | Czech Republic | Caucasian | Prague 50°05’N  | T2DM    | 11      | 58      | 63      | 12         | 76         | 25         |
| Wehr E          | 2011 | Austria | Caucasian       | Graz 47°4’N       | PCOS    | 82      | 241     | 215     | 22         | 60         | 53         |
| Xia Z           | 2014 | China   | Asian           | Beijing 39°26’-41°03’N | T2DM    | 19      | 94      | 124     | 9          | 47         | 35         |
| Yi Zhao         | 2014 | China   | Asian           | Yinchuan, Ningxia 38°2’N | MetS    | 75      | 184     | 132     | 80         | 207        | 112        |
| Zhong X         | 2015 | China   | Asian           | Anhui Province 31°52’N | T2DM    | 44      | 114     | 46      | 18         | 58         | 40         |
Table 5 Summary of meta-analysis

| Comparison of outcome | No. of trials | No. of Case | No. of Control | Effect size (95% confidence intervals) | \( P \) | Test for heterogeneity |
|-----------------------|--------------|-------------|----------------|----------------------------------------|-------|-----------------------|
|                       |              |             |                | \( P \) Test for heterogeneity          | \( I^2 \) \( \% \) | \( P \) |
| **ApaI**              |              |             |                |                                        |       |                       |
| GG/GT + TT 14         | 3212         | 3360        |                | 1.08 [0.91, 1.28]                      | 0.37 | 30 0.14               |
| T2DM 9                | 2017         | 2555        |                | 1.00 [0.78, 1.28]                      | 1     | 51 0.05               |
| PCOS 5                | 1195         | 805         |                | 1.15 [0.88, 1.50]                      | 0.31 | 0 0.47                |
| GG + GT/TT 14         | 3212         | 3360        |                | 1.04 [0.89, 1.21]                      | 0.62 | 38 0.08               |
| T2DM 9                | 2017         | 2555        |                | 0.93 [0.79, 1.11]                      | 0.44 | 17 0.29               |
| PCOS 5                | 1195         | 805         |                | 1.15 [0.90, 1.45]                      | 0.27 | 30 0.22               |
| G allele 14           | 3212         | 3360        |                | 1.04 [0.95, 1.14]                      | 0.36 | 26 0.18               |
| T2DM 9                | 2017         | 2555        |                | 0.97 [0.85, 1.11]                      | 0.7  | 42 0.1                |
| PCOS 5                | 1195         | 805         |                | 1.11 [0.96, 1.27]                      | 0.15 | 0 0.84                |
| T allele 14           | 3212         | 3360        |                | 1.02 [0.91, 1.15]                      | 0.7  | 56 0.0005             |
| T2DM 9                | 2017         | 2555        |                | 1.03 [0.90, 1.18]                      | 0.68 | 43 0.09               |
| PCOS 5                | 1195         | 805         |                | 1.07 [0.83, 1.37]                      | 0.62 | 70 0.01               |
| **Ethnic**            |              |             |                |                                        |       |                       |
| GG/GT + TT 13         | 3087         | 3235        |                | 1.09 [0.91, 1.30]                      | 0.34 | 34 0.11               |
| Caucasian 5           | 1488         | 1929        |                | 1.20 [0.99, 1.45]                      | 0.06 | 0 0.41                |
| Caucasian (dark) 6    | 1091         | 1090        |                | 0.94 [0.64, 1.36]                      | 0.73 | 52 0.07               |
| Asian 2               | 508          | 216         |                | 1.24 [0.88, 1.76]                      | 0.22 | 0 0.88                |
| GG + GT/TT 13         | 3087         | 3235        |                | 1.08 [0.94, 1.24]                      | 0.29 | 21 0.23               |
| Caucasian 5           | 1488         | 1929        |                | 1.13 [0.87, 1.46]                      | 0.36 | 49 0.1                |
| Caucasian (dark) 6    | 1091         | 1090        |                | 0.97 [0.81, 1.15]                      | 0.7  | 0 0.89                |
| Asian 2               | 508          | 216         |                | 1.62 [1.03, 2.53]                      | 0.04 | 0 0.35                |
| G allele 13           | 3087         | 3235        |                | 1.06 [0.98, 1.16]                      | 0.16 | 13 0.31               |
| Caucasian 5           | 1488         | 1929        |                | 1.11 [0.98, 1.27]                      | 0.06 | 0 0.51                |
| Caucasian (dark) 6    | 1091         | 1090        |                | 0.96 [0.85, 1.09]                      | 0.51 | 0 0.66                |
| Asian 2               | 508          | 216         |                | 1.25 [0.99, 1.57]                      | 0.1  | 17 0.3                |
| T allele 13           | 3087         | 3235        |                | 1.01 [0.89, 1.14]                      | 0.93 | 56 0.0008             |
| Caucasian 5           | 1488         | 1929        |                | 0.94 [0.80, 1.09]                      | 0.4  | 42 0.14               |
| Caucasian (dark) 6    | 1091         | 1090        |                | 1.16 [0.97, 1.38]                      | 0.1  | 47 0.0009             |
| Asian 2               | 508          | 216         |                | 0.80 [0.64, 1.01]                      | 0.06 | 0 0.51                |
| **Latitude**          |              |             |                |                                        |       |                       |
| GG/GT + TT 14         | 3212         | 3360        |                | 1.08 [0.91, 1.28]                      | 0.37 | 30 0.14               |
| Low (<30) 5           | 1136         | 834         |                | 0.86 [0.65, 1.14]                      | 0.3  | 19 0.29               |
| Middle (30–60) 9      | 2076         | 2526        |                | 1.22 [1.04, 1.43]                      | 0.02 | 0 0.43                |
| GG + GT/TT 14         | 3212         | 3360        |                | 1.04 [0.89, 1.21]                      | 0.62 | 38 0.08               |
| Low (<30) 5           | 1136         | 834         |                | 0.91 [0.73, 1.15]                      | 0.44 | 17 0.31               |
| Middle (30–60) 9      | 2076         | 2526        |                | 1.12 [0.92, 1.36]                      | 0.27 | 42 0.08               |
| G allele 14           | 3212         | 3360        |                | 1.04 [0.95, 1.14]                      | 0.36 | 26 0.18               |
| Low (<30) 5           | 1136         | 834         |                | 0.92 [0.80, 1.07]                      | 0.27 | 10 0.35               |
| Middle (30–60) 9      | 2076         | 2526        |                | 1.12 [1.01, 1.23]                      | 0.02 | 0 0.44                |
| T allele 14           | 3212         | 3360        |                | 1.02 [0.91, 1.15]                      | 0.7  | 56 0.0005             |
| Low (<30) 5           | 1136         | 834         |                | 1.09 [0.94, 1.25]                      | 0.26 | 10 0.35               |
| Middle (30–60) 9      | 2076         | 2526        |                | 0.99 [0.84, 1.18]                      | 0.95 | 66 0.003              |
| **BsmI**              |              |             |                |                                        |       |                       |
| AA/GA + GG 22         | 4294         | 4157        |                | 0.95 [0.78, 1.16]                      | 0.64 | 41 0.02               |
| T2DM 14               | 2802         | 3051        |                | 0.99 [0.75, 1.31]                      | 0.93 | 55 0.0007             |
| Variable | # | Value 1 | Value 2 | OR  | CI    | P   | OR  | CI    | P   |
|---------|---|---------|---------|-----|-------|-----|-----|-------|-----|
| PCOS    | 4 | 835     | 443     | 1.11| [0.77, 1.58] | 0.58| 0   | 0.61  |     |
| MetS    | 4 | 657     | 663     | 0.72| [0.50, 1.05]  | 0.09| 0   | 0.5   |     |
| AA + GA/GG | 22 | 4294 | 4157 | 1.06| [0.86, 1.31]  | 0.59| 69  | <0.00001 |     |
| T2DM    | 14| 2802    | 3051    | 1.19| [0.90, 1.57]  | 0.21| 71  | <0.001 |     |
| PCOS    | 4 | 835     | 443     | 1.06| [0.79, 1.36]  | 0.65| 12  | 0.29  |     |
| MetS    | 4 | 657     | 663     | 0.62| [0.45, 0.86]  | 0.005| 11  | 0.34  |     |
| A allele | 22 | 4294 | 4157 | 1.08| [0.89, 1.32]  | 0.42| 83  | <0.00001 |     |
| T2DM    | 14| 2802    | 3051    | 1.05| [0.85, 1.28]  | 0.67| 76  | <0.00001 |     |
| PCOS    | 4 | 835     | 443     | 0.96| [0.79, 1.16]  | 0.65| 12  | 0.33  |     |
| MetS    | 4 | 657     | 663     | 0.71| [0.54, 0.93]  | 0.01| 37  | 0.19  |     |
| G allele | 22 | 4294 | 4157 | 1.08| [0.89, 1.32]  | 0.42| 83  | <0.00001 |     |

**Ethnic**

| Ethnic     | # | Value 1 | Value 2 | OR  | CI    | P   | OR  | CI    | P   |
|------------|---|---------|---------|-----|-------|-----|-----|-------|-----|
| AA/GA + GG | 21| 4194    | 4057    | 0.98| [0.80, 1.21] | 0.87| 40  | 0.03  |     |
| Caucasian  | 7 | 1683    | 2121    | 1.01| [0.81, 1.26] | 0.92| 9   | 0.36  |     |
| Caucasian (dark) | 7 | 913    | 793     | 1.05| [0.82, 1.35] | 0.69| 0   | 0.82  |     |
| Asian      | 7 | 1598    | 1143    | 0.90| [0.39, 2.08]  | 0.81| 67  | 0.006 |     |
| AA + GA/GG | 21| 4194    | 4057    | 1.10| [0.89, 1.36] | 0.38| 68  | <0.00001 |     |
| Caucasian  | 7 | 1683    | 2121    | 0.98| [0.82, 1.18] | 0.84| 25  | 0.24  |     |
| Caucasian (dark) | 7 | 913    | 793     | 1.50| [1.16, 1.93] | 0.002| 19  | 0.29  |     |
| Asian      | 7 | 1598    | 1143    | 0.89| [0.49, 1.61] | 0.69| 80  | <0.00001 |     |
| A allele   | 21| 4194    | 4057    | 1.02| [0.87, 1.19] | 0.84| 72  | <0.00001 |     |
| Caucasian  | 7 | 1683    | 2121    | 1.03| [0.86, 1.23] | 0.75| 59  | 0.02  |     |
| Caucasian (dark) | 7 | 913    | 793     | 1.23| [1.07, 1.42] | 0.004| 0   | 0.91  |     |
| Asian      | 7 | 1598    | 1143    | 0.81| [0.49, 1.34] | 0.42| 86  | <0.00001 |     |
| G allele   | 21| 4194    | 4057    | 1.06| [0.87, 1.29] | 0.57| 83  | <0.00001 |     |
| Caucasian  | 7 | 1683    | 2121    | 1.19| [0.85, 1.65] | 0.32| 89  | <0.00001 |     |
| Caucasian (dark) | 7 | 913    | 793     | 0.81| [0.70, 0.94] | 0.004| 0   | 0.91  |     |
| Asian      | 7 | 1598    | 1143    | 1.23| [0.74, 2.04] | 0.42| 86  | <0.00001 |     |

**Latitude**

| Latitude   | # | Value 1 | Value 2 | OR  | CI    | P   | OR  | CI    | P   |
|------------|---|---------|---------|-----|-------|-----|-----|-------|-----|
| AA/GA + GG | 22| 4294    | 4157    | 0.95| [0.78, 1.16] | 0.64| 41  | 0.02  |     |
| Low (<30)  | 5 | 912     | 659     | 0.74| [0.52, 1.05] | 0.09| 39  | 0.16  |     |
| Middle (30–60) | 17| 3382 | 3498 | 1.05| [0.83, 1.33] | 0.68| 37  | 0.06  |     |
| AA + GA/GG | 22| 4294    | 4157    | 1.06| [0.86, 1.31] | 0.59| 69  | <0.00001 |     |
| Low (<30)  | 5 | 912     | 659     | 1.32| [0.73, 2.38] | 0.35| 70  | 0.009 |     |
| Middle (30–60) | 17| 3382 | 3498 | 1.00| [0.81, 1.23] | 0.97| 61  | 0.0005 |     |
| A allele   | 22| 4294    | 4157    | 0.97| [0.83, 1.13] | 0.67| 72  | <0.00001 |     |
| Low (<30)  | 5 | 912     | 659     | 0.96| [0.64, 1.43] | 0.83| 80  | 0.0005 |     |
| Middle (30–60) | 17| 3382 | 3498 | 0.97| [0.82, 1.15] | 0.7  | 70  | <0.00001 |     |
| G allele   | 22| 4294    | 4157    | 1.08| [0.89, 1.32] | 0.42| 83  | <0.00001 |     |
| Low (<30)  | 5 | 912     | 659     | 1.04| [0.80, 1.36] | 0.83| 80  | 0.0005 |     |
| Middle (30–60) | 17| 3382 | 3498 | 1.09| [0.87, 1.37] | 0.44| 84  | <0.00001 |     |

**TaqI**

| TaqI     | # | Value 1 | Value 2 | OR  | CI    | P   | OR  | CI    | P   |
|----------|---|---------|---------|-----|-------|-----|-----|-------|-----|
| TT/TC + CC | 19| 3533    | 4024    | 1.00| [0.82, 1.21] | 0.96| 60  | 0.004 |     |
| T2DM     | 13| 2305    | 3187    | 1.09| [0.84, 1.42] | 0.51| 60  | 0.003 |     |
| PCOS     | 6 | 1228    | 837     | 0.86| [0.62, 1.20] | 0.37| 65  | 0.01  |     |
Table 5 Summary of meta-analysis (Continued)

| Ethic | TT + TC/CC | T2DM | PCOS | T allele | T2DM | PCOS | C allele | T2DM | PCOS |
|-------|------------|------|------|----------|------|------|----------|------|------|
|       | 19         | 3533 | 4024 | 0.88     | 0.17 | 43   | 0.02     |      |      |
|       | 13         | 2305 | 3187 | 0.92     | 0.43 | 41   | 0.06     |      |      |
|       | 6          | 1228 | 837  | 0.77     | 0.22 | 52   | 0.06     |      |      |
|       | 19         | 3533 | 4024 | 0.89     | 0.18 | 79   | <0.0001  |      |      |
|       | 13         | 2305 | 3187 | 1.01     | 0.95 | 60   | 0.03     |      |      |
|       | 6          | 1228 | 837  | 0.68     | 0.03 | 84   | <0.0001  |      |      |
|       | 19         | 3533 | 4024 | 1.13     | 0.18 | 79   | <0.0001  |      |      |
| Ethnic |            |      |      |          |      |      |          |      |      |
| T2DM  | 17         | 3368 | 3859 | 0.93     | 0.45 | 49   | 0.01     |      |      |
| PCOS  | 7          | 1653 | 2190 | 1.10     | 0.35 | 38   | 0.14     |      |      |
|       | 7          | 1159 | 1121 | 0.75     | 0.03 | 46   | 0.08     |      |      |
|       | 3          | 556  | 548  | 1.94     | 0.47 | 0    | 0.44     |      |      |
|       | 17         | 3368 | 3859 | 0.88     | 0.2  | 48   | 0.01     |      |      |
|       | 7          | 1653 | 2190 | 1.12     | 0.47 | 50   | 0.06     |      |      |
|       | 7          | 1159 | 1121 | 0.76     | 0.07 | 39   | 0.13     |      |      |
|       | 3          | 556  | 548  | 0.67     | 0.03 | 0    | 0.4      |      |      |
|       | 17         | 3368 | 3859 | 0.84     | 0.06 | 78   | <0.00001 |      |      |
|       | 7          | 1653 | 2190 | 0.94     | 0.73 | 90   | <0.00001 |      |      |
|       | 7          | 1159 | 1121 | 0.80     | 0.01 | 41   | 0.12     |      |      |
|       | 3          | 556  | 548  | 0.73     | 0.08 | 10   | 0.33     |      |      |
|       | 17         | 3368 | 3859 | 1.18     | 0.06 | 78   | <0.00001 |      |      |
|       | 7          | 1653 | 2190 | 1.06     | 0.73 | 90   | <0.00001 |      |      |
|       | 7          | 1159 | 1121 | 1.24     | 0.01 | 42   | 0.11     |      |      |
|       | 3          | 556  | 548  | 1.37     | 0.08 | 10   | 0.33     |      |      |
| Latitude |          |      |      |          |      |      |          |      |      |
| TT/TC + CC | 18     | 3493 | 3984 | 0.95     | 0.52 | 47   | 0.02     |      |      |
|       | 5          | 934  | 896  | 0.86     | 0.2  | 24   | 0.26     |      |      |
|       | 13         | 2559 | 3088 | 1.00     | 0.97 | 52   | 0.01     |      |      |
|       | 18         | 3493 | 3984 | 0.87     | 0.15 | 45   | 0.02     |      |      |
|       | 5          | 934  | 896  | 0.88     | 0.3  | 0    | 0.44     |      |      |
|       | 13         | 2559 | 3088 | 0.87     | 0.29 | 56   | 0.007    |      |      |
| T allele | 18         | 3493 | 3984 | 0.85     | 0.06 | 77   | <0.00001 |      |      |
|       | 5          | 934  | 896  | 0.90     | 0.11 | 0    | 0.69     |      |      |
|       | 13         | 2559 | 3088 | 0.84     | 0.15 | 83   | <0.00001 |      |      |
|       | 18         | 3493 | 3984 | 1.17     | 0.06 | 77   | <0.00001 |      |      |
|       | 5          | 934  | 896  | 1.11     | 0.12 | 0    | 0.68     |      |      |
|       | 13         | 2559 | 3088 | 1.19     | 0.15 | 83   | <0.00001 |      |      |
| Fok1  | CC/CT + TT | 18   | 4992 | 6230 | 1.03 | 0.79 | 80 <0.00001 |      |      |
|       | 9          | 1086 | 690  | 1.10 | 0.63 | 81 | <0.00001 |      |      |
|       | 5          | 631  | 559  | 1.20 | 0.46 | 93 | <0.00001 |      |      |
|       | 3          | 1084 | 1960 | 0.60 | 0.46 | 93 | <0.00001 |      |      |
|       | 18         | 4992 | 6230 | 0.92 | 0.49 | 74 | <0.00001 |      |      |
|       | 9          | 1086 | 690  | 1.02 | 0.88 | 58 | 0.01     |      |      |
|       | 5          | 631  | 559  | 1.29 | 0.27 | 41 | 0.15     |      |      |
|       | 3          | 1084 | 1960 | 0.35 | 0.09 | 93 | <0.00001 |      |      |
polymorphism was more important with PCOS and MetS than T2DM. However, sub-group analysis showed VDR ApaI variant was associated with insulin resistance related diseases in Asians, VDR BsmI and VDR TaqI variant was associated with insulin resistance related diseases in Caucasian (dark-pigmented). The results suggested that the association between insulin resistance related diseases and VDR ApaI, BsmI, FokI variant was more obvious in dark-pigmented Caucasians and Asians but not in Caucasian with white skin.

Abbreviations
MetS: Metabolic syndrome; PCOS: Polycystic ovarian syndrome; T2DM: Type 2 diabetes; VDR: Vitamin D receptor

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Availability of data and materials
Please contact author for data requests.

Table 5 Summary of meta-analysis (Continued)

| C allele | T2DM | PCOS | MetS | T allele | T2DM | PCOS | MetS |
|----------|------|------|------|----------|------|------|------|
|          | 18   | 4992 | 6230 | 0.99    | 0.84 | 73   | <0.00001 |
|          | 9    | 1086 | 690  | 1.00    | 0.99 | 81   | <0.00001 |
|          | 5    | 631  | 559  | 1.09    | 0.49 | 54   | 0.07  |
|          | 3    | 1084 | 1960 | 0.75    | 0.18 | 72   | 0.03  |
|          | 18   | 4992 | 6230 | 1.01    | 0.85 | 73   | <0.00001 |
|          | 9    | 1086 | 690  | 1.00    | 0.99 | 81   | <0.00001 |
|          | 5    | 631  | 559  | 0.92    | 0.49 | 54   | 0.07  |
|          | 3    | 1084 | 1960 | 1.33    | 0.19 | 73   | 0.03  |

Ethnic

| C/C + CT/TT | Low (<30) | Middle (30–60) | Low (<30) | Middle (30–60) | CC/CT + TT | Low (<30) | Middle (30–60) | Low (<30) | Middle (30–60) |
|-------------|-----------|---------------|-----------|---------------|------------|-----------|---------------|-----------|---------------|
| C allele    |           |               |           |               |            |           |               |           |               |
| Low (<30)   | 5         | 852           | 791       | 1.00          | 0.99       | 52        | 0.08          |           |               |
| Middle (30–60) | 18     | 4992          | 6230      | 1.03          | 0.79       | 80        | <0.00001      |           |               |
| Low (<30)   | 5         | 852           | 791       | 0.78          | 0.60       | 74        | 0.03          |           |               |
| Middle (30–60) | 13     | 4140          | 5439      | 0.94          | 0.69       | 66        | <0.00001      |           |               |
| CC + CT/TT  |           |               |           |               |            |           |               |           |               |
| Low (<30)   | 5         | 852           | 791       | 0.91          | 0.74       | 33        | 0.2           |           |               |
| Middle (30–60) | 13     | 4140          | 5439      | 1.01          | 0.86       | 78        | <0.00001      |           |               |
| T allele    |           |               |           |               |            |           |               |           |               |
| Low (<30)   | 5         | 852           | 791       | 1.10          | 0.90       | 36        | 0.2           |           |               |

Latitude

| C allele    | T2DM | PCOS | MetS | T allele | T2DM | PCOS | MetS |
|-------------|------|------|------|----------|------|------|------|
| Low (<30)   | 5    | 852  | 791  | 1.00    | 0.99 | 52   | 0.08  |
| Middle (30–60) | 13   | 4140 | 5439 | 1.03    | 0.82 | 80   | <0.00001 |
| Low (<30)   | 5    | 852  | 791  | 0.78    | 0.60 | 80   | <0.00001 |
| Middle (30–60) | 13   | 4140 | 5439 | 0.94    | 0.69 | 80   | <0.00001 |
| C allele    | T2DM | PCOS | MetS | T allele | T2DM | PCOS | MetS |
| Low (<30)   | 5    | 852  | 791  | 0.91    | 0.74 | 33   | 0.2   |
| Middle (30–60) | 13   | 4140 | 5439 | 1.01    | 0.86 | 78   | <0.00001 |
| T allele    | Low (<30) | Middle (30–60) | Low (<30) | Middle (30–60) | C allele | Low (<30) | Middle (30–60) | Low (<30) | Middle (30–60) |
| Low (<30)   | 5    | 852  | 791  | 1.10    | 0.90 | 36   | 0.2   |           |               |
| Middle (30–60) | 13   | 4140 | 5439 | 0.99    | 0.85 | 78   | <0.00001 |           |               |

Abbreviations
MetS: Metabolic syndrome; PCOS: Polycystic ovarian syndrome; T2DM: Type 2 diabetes; VDR: Vitamin D receptor

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Availability of data and materials
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Authors’ contributions
FH designed the study and revised the manuscript, FH and YL extracted the data, LG, ZW, LL, HL verified the data. FH researched the data and wrote the manuscript. FH contributed to interpreting the results, draft reviewing, and finalizing the manuscript. All authors read and approved the final manuscript.

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References
1. Ning Z, Song S, Miao L, Zhang P, Wang X, Liu J, Hu Y, Xu Y, Zhao T, Liang Y, et al. High prevalence of vitamin D deficiency in urban health checkup population. Clin Nutr. 2015;35:859–63.
2. Peterson CA, Tosh AK, Belencha AM. Vitamin D insufficiency and insulin resistance in obese adolescents. Ther Adv Endocrinol Metab. 2014;5:166–89.
3. Dass Gupta S, Dutta J, Annamalai S, Kudugunti N, Battini MR. Association of vitamin D receptor gene polymorphisms with polycystic ovary syndrome among Indian women. Indian J Med Res. 2015;142:276–85.
4. Lee S, Clark SA, Gill RK, Chistkas S, S1, 25-Dihydroxyvitamin D3 and pancreatic beta-cell function: vitamin D receptors, gene expression, and insulin secretion. Endocrinology. 1994;134:1602–10.
5. Pittas AG, Sun Q, Manson JE, Dawson-Hughes B, Hu FB. Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. Diabetes Care. 2010;33:2021–3.
6. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the third National Health and nutrition examination survey. Diabetes Care. 2004;27:2813–8.
7. Liu E, Meigs JB, Pittas AG, Economos CD, Mckeeown NM, Booth SL, Jacques PF. Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham offspring study. Am J Clin Nutr. 2010;91:1627–33.
8. Zhang Q, Cheng Y, He M, Li T, Ma Z, Cheng H. Effect of various doses of vitamin D supplementation on pregnant women with gestational diabetes mellitus: a randomized controlled trial. Exp Ther Med. 2016;12:1889–95.
9. Zhang J, Ye J, Guo G, Lan Z, Li X, Fan Z, Rao X, Zhang Z. Vitamin D Status is Negatively Correlated with Insulin Resistance in Chinese Type 2 Diabetes. Int J Endocrinol. 2016;2016:1794894.
10. Sung KC, Chang Y, Ryu S, Chung HK. High levels of serum vitamin D are associated with a decreased risk of metabolic diseases in both men and women, but an increased risk for coronary artery calcification in Korean men. Cardiovasc Diabetol. 2016;15:112.
11. Højlund K. Metabolism and insulin signaling in common metabolic disorders and inherited insulin resistance. Dan Med J. 2014;61:B4890.
12. Grundy SM. Metabolic syndrome update. Trends Cardiovasc Med. 2016;26:364-73.
13. Krul-Poel YH, Snackey C, Louwers Y, Lips P, Lambalk CB, Laven JS, Simsek S. The role of vitamin D in metabolic disturbances in polycystic ovary syndrome: a systematic review. Eur J Endocrinol. 2013;169:653–65.
14. Chale A, Chale C. Color by numbers: when population skin pigmentation is not political but a polytactical evaluation exercise to measure vitamin D, diseases, and skin pigmentation. J Acad Nutr Diet. 2016;116:1251–6.
15. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. J Nutr. 2005;135:310–6.
16. Moore CE, Murphy MM, Holick MF. Vitamin D intakes by children and adults in the United States differ among ethnic groups. J Nutr. 2005;135:2478–85.
17. Yuan W, Xu L, Feng Y, Yang Y, Chen W, Wang J, Pang D, Li D. The hOG1Ser262Cys polymorphism and breast cancer risk: a meta-analysis. Breast Cancer Res Treat. 2010;122:835–42.
18. Al-Daghri NM, Al-Attas O, Alokail MS, Alkhary KM, Draz HM, Alghawi C, Mohammed AK, Guerini FR, Clerici M. Vitamin D receptor gene polymorphisms and HDL DRB*0104 cosegregation in Saudi type 2 diabetes patients. J Immunol. 2012;188:1325–32.
19. Boullu-Sanchis S, Lepere F, Hedelin G, Donnet JP, Schaffer P, Froquel P, Pinget M. Type 2 diabetes mellitus: association study of five candidate genes in an Indian population of Guadeloupe, genetic contribution of FABP2 polymorphism. Diabetes Metab. 1999;25:150–6.
20. El-Shal AS, Shalaby SM, Al-N M, Rashad NM, Abdelaziz AM. Genetic variation in the vitamin D receptor gene and vitamin D serum levels in Egyptian women with polycystic ovary syndrome. Mol Biol Rep. 2013;40:603–73.
21. Dilmec F, Uzer E, Akkafa E, Kose E, van Kullenburg AB. Detection of VDR gene Apal and TaqI polymorphisms in patients with type 2 diabetes mellitus using PCR-RFLP method in a Turkish population. J Diabetes Complicat. 2010;24:896–91.
22. Oh JF, Barent-Coron E. Association between vitamin D receptor polymorphism and type 2 diabetes or metabolic syndrome in community-dwelling older adults: the rancho Bernardo study. Metabolism. 2002;51:356–9.
23. Jedrzejuk D, Laczemski L, Milewicz A, Kuczlikowska-Plasek J, Lenarcik-Kabza A, Hitme L, Zaleska-Dorobisz U, Lwow F. Classic PCOS phenotype is not associated with deficiency of endogenous vitamin D and VDR gene polymorphisms rs731236 (Taql), rs7975232 (Apal), rs1544410 (BsmI), rs10735810 (FokI): a case–control study of lower Silesian women. Gynecol Endocrinol. 2015;31:976–9.
24. Mahmoudi T. Genetic variation in the vitamin D receptor and polycystic ovary syndrome risk. Fertil Steril. 2009;92:1381–3.
25. Malecki MT, Frey J, Moczulski D, Klupa T, Kozek E, Sieradzki J. Vitamin D receptor gene polymorphisms and association with type 2 diabetes mellitus in a polish population. Exp Clin Endocrinol Diabetes. 2003;11:505–9.
26. Rivera-Leon EA, Palmeros-Sanchez B, Llamas-Covarrubias IW, Fernandez S, Ammandariz-Borunda J, Gonzalez-Hita M, Bastidas-Ramirez BE, Zepeda-Moreno A, Sanchez-Enriquez S. Vitamin-D receptor gene polymorphisms (TaqI and Apal) and circulating osteocalcin in patients with type 2 diabetes and healthy subjects. Endokrynologia Polska. 2015;66:329–33.
27. Wehr E, Trummer O, Giuliani A, Gruber HJ, Pieper TK, Obermayer-Pietsch B. Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. Eur J Endocrinol. 2011;164:741–9.
28. Ye WZ, Reis AF, Dubois-Laforgue D, Bellanne-Chantelot C, Timst J, Velho G. Vitamin D receptor gene polymorphisms are associated with obesity in type 2 diabetic subjects with early age of onset. Eur J Endocrinol. 2001;145:181–6.
29. Zhang H, Wang J, Yi B, Zhao Y, Liu Y, Zhang K, Cai X, Sun J, Huang L, Liao Q, BsmI polymorphisms in vitamin D receptor gene are associated with diabetic nephropathy in type 2 diabetes patients. PLoS One. 2015;10:e0122116–6.
30. Baghetti M, Rad IA, Jazani NH, Nanaikbsh F. Lack of Association of Vitamin D Receptor FokI rs10735810 (C/T) and BsmI rs1544410 (A/G) genetic variations with polycystic ovary syndrome risk: a case–control study from Iranian Azeri Turkish women. Maedica (Buchar). 2012;7:303–8.
31. Bid HK, Konwar R, Aggarwal CG, Gautam S, Saxena M, Niyak VL, Banerjee M, Vitamin D receptor (FokI, BsmI and TaqI) gene polymorphisms and type 2 diabetes mellitus: A North Indian study. Indian J Med Sci. 2009;63:167–94.
32. Mukhopadhyaya PN, Achariya A, Chavan Y, Purohit SS, Mutha A. Metagenomic study of single-nucleotide polymorphism within candidate genes associated with type 2 diabetes in an Indian population. Genet Mol Res. 2010;9:2060–8.
33. Speer C, Cieh K, Winkler G, Vargha P, Braun E, Takacs I, Lakatos P. Vitamin D and estrogen receptor gene polymorphisms in type 2 diabetes mellitus and in android type obesity. Eur J Endocrinol. 2001;144:385–9.
34. Vural HC, Mutas E. RT-qPCR assay on the vitamin D receptor gene in type 2 diabetes and hypertoners patients in Turkey. Genet Mol Res. 2012;11:582–90.
35. Xia Z, Hu Y, Zhang H, Han Z, Bai J, Fu S, Deng X, He Y. Association of vitamin D receptor FokI and BsmI polymorphisms with dyslipidemias in elderly male patients with type 2 diabetes. Nan Fang Yi Ke Da Xue Xue Bao. 2014;34:1562–8.
36. Xu JR, Lu YB, Geng HF, Wu J, Maio H. Association between the polymorphism of human vitamin D receptor gene and type2 diabetes. J Clin Rehabil Tissue Eng Res. 2007;11:5881–3.
37. Xu JR, Na XF, Yang Y. Relevance analysis on polymorphisms of four SNPs of VDR gene and type 2 diabetes mellitus in Ningxia Han population. J Iljin Univ Med Ed. 2012;38:985–9.
39. Xu JR, Yang Y, Liu XM, Wang YJ. Association of VDR polymorphisms with type 2 diabetes mellitus in Chinese Han and Hui populations. Genet Mol Res. 2014;13:9588–98.

40. Bagheri M, Abdali Rad I, Hosseini Jazani N, Nanbaksh F. Vitamin D receptor taqI gene variant in exon 9 and polycystic ovary syndrome risk. Int J Fert Ster. 2013;7:16–21.

41. Jia J, Ding H, Yang K, Mao L, Zhao H, Zhan Y, Shen C. Vitamin D receptor genetic polymorphism is significantly associated with risk of type 2 diabetes mellitus in Chinese Han population. Arch Med Res. 2015;46:572–9.

42. Schuch NJ, Garcia VC, Vivolo SR, Martini LA. Relationship between vitamin D receptor gene polymorphisms and the components of metabolic syndrome. Nutr J. 2013;12:96.

43. Shah DB, Doshi DD, Singh KM, Patel RK. Investigation of the VDR gene polymorphism in unrelated gujarati group with and without diabetic mellitus type-2. Res J Pharm, Biol Chem Sci. 2015;6:465–8.

44. Vedralová M, Kotrbhova-Kozak A, Zeleznisková V, Zoubková H, Rychlik I, Černá M. Polymorphisms in the vitamin D receptor gene and parathyroid hormone gene in the development and progression of diabetes mellitus and its chronic complications, diabetic nephropathy and non-diabetic renal disease. Kidney Blood Press Res. 2012;36:1–9.

45. Zhao Y, Liao S, He J, Jin Y, Fu H, Chen X, Fan X, Xu H, Liu X, Jin J, Zhang Y. Association of vitamin D receptor gene polymorphisms with metabolic syndrome: a case–control design of population-based cross-sectional study in North China. Lipids Health Dis. 2014;13:129.

46. Ellison TI, Dowd DR, MacDonald PN. Calmodulin-dependent kinase IV stimulates vitamin D receptor-mediated transcription. Mol Endocrinol. 2005;19:2309–19.

47. Oh J, Riek AE, Danwech I, Funai K, Shao J, Chin K, Sierra DL, Carmeliet G, Ostlund RE Jr, Bernal-Mizrachi C. Deletion of macrophage vitamin D receptor promotes insulin resistance and monocyte cholesterol transport to accelerate atherosclerosis in mice. Cell Rep. 2015;10:1872–86.

48. Shilpi Dasgupta, Joyita Dutta, Sandhya Annamaneni, Neelaveni Kudugunti, MohanReddy Battini. Association of vitamin D receptor gene polymorphisms with polycystic ovary syndrome among Indian women. Indian J Med Res. 2015;142(3):276.

49. Rivera-Leon EA, Palmeros-Sanchez B, Llamas-Covarrubias IM, Fernandez S, Amendiaz-Borunda J, Gonzalez-Hita M, Bastidas-Ramirez BE, Zepeda-Moreno A, Sanchez-Enriquez S. Vitamin-D receptor gene polymorphisms (Taq1 and Apa1) and circulating osteocalcin in type 2 diabetic patients and healthy subjects. Endokrynol Pol. 2015;66:329–33.

50. Mackawy AMH, Badawi, MEH. Association of vitamin D and vitamin D receptor gene polymorphisms with chronic inflammation, insulin resistance and metabolic syndrome components in type 2 diabetic Egyptian patients. Meta Gene. 2014;2:540–56.