

# Blood Lipid Levels in Patients with Osteopenia and Osteoporosis: A Systematic Review and Meta-Analysis

**Hang Zhao**

hebei genral hospital

**An Song**

Hebei General Hospital

**Yong Li**

Hebei General Hospital

**Licui Qi**

Hebei General Hospital

**Chong Zheng**

Shijiazhuang third hospital

**Luping Ren**

Hebei General Hospital

**Guangyao Song** (✉ [guangyaosong123@163.com](mailto:guangyaosong123@163.com))

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## Research

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# Abstract

**Background:** Considering the controversial relationship between blood lipid levels and osteopenia and osteoporosis (OP), we performed this meta-analysis.

**Methods:** Using specific keywords and related words, we searched PubMed, Embase, and Cochrane Library databases. The Newcastle-Ottawa Scale form was used to evaluate the quality of the literature. According to the inclusion and exclusion criteria, we systematically screened the literature to extract relevant information and data. Revman 5.3 and Stata 13.0 software were used for statistical analysis. Results were expressed as the mean difference and 95% confidence interval. The heterogeneity test was conducted according to  $I^2$  and Q tests. Egger's test was used to quantitatively evaluate publication bias.

**Results:** This analysis involved 12 studies and included 12,395 subjects. The quality of the literature was acceptable. Among subjects who were not taking lipid-lowering drugs, total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) in the osteopenia were not significantly increased/decreased. There were no significant differences in LDL-C in postmenopausal women in osteopenia. TG was unchanged in the OP group in subjects without taking lipid-lowering drugs. HDL-C was elevated in OP group but not in osteopenia group in all subjects

**Conclusions:** HDL-C was elevated in patients with OP.

## 1 Background

Osteoporosis (OP) is a disease characterized by reduced bone mineral density (BMD) and an increased risk of osteoporotic fractures. It is one of the most common metabolic diseases in the elderly population. This poses a serious health concern worldwide<sup>[1]</sup> because osteoporotic fractures are the leading cause of disability and death in elderly patients<sup>[2]</sup>. The onset of this disease is associated with various factors, including aging, gender, insufficient calcium intake, vitamin D deficiency, low body mass index (BMI), decreased physical activity<sup>[3]</sup>, and hyperthyroidism<sup>[4]</sup>. Among them, nutrition is one of the most important factors. When malnutrition occurs, the raw materials for bone formation are limited, which can lead to the development of osteopenia and even OP. BMI is an indicator used to assess nutritional status. Previous studies have shown that people with a high BMI have a low risk of OP<sup>[5]</sup>. It has been suggested that blood lipid levels also reflect the nutrition level to some extent, but in patients with osteopenia or OP, the results of various studies on blood lipid levels have been inconclusive. Gu et al.<sup>[6]</sup> found that compared with the control group, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were significantly increased in adult patients with osteopenia and OP. Ersoy's<sup>[7]</sup> study indicated that TC and LDL-C were decreased in postmenopausal women with OP. However, Li<sup>[8]</sup> found that TC, triglyceride (TG), and LDL-C levels were not significantly different in postmenopausal women with OP. Therefore, the blood lipid levels in patients with osteopenia, or OP remain unknown. In addition, whether an increase in blood lipid levels can protect patients from the development of OP is not well understood. The aim of this meta-analysis was to extract blood lipid indicators in patients with osteopenia, or OP from case-control studies and to determine their levels.

## 2 Methods

### 2.1 Search strategy

Two researchers used subject words and free words, including "bone mineral density", "osteoporosis", "fractures", "bone", and "lipids", to search PubMed, Embase, and Cochrane databases (**Supplementary material 1**). We also manually checked the references listed in the retrieved references to prevent missing studies. The search was limited to English language and deadline was February 2020. For articles with only titles and abstracts, we requested articles by email. The inclusion and exclusion criteria were as follows.

### 2.2 Inclusion criteria

- i) The article involved at least one of osteopenia and osteoporosis, and the diagnostic criteria were clear.
- ii) The article involved at least one of the following blood lipids: TC, TG, high-density lipoprotein cholesterol (HDL-C), or LDL-C.
- iii) The study was a case-control study.
- iv) The literature provided original data or relevant data that could be obtained based on data conversion.

## 2.3 Exclusion criteria

- i) The subjects had acute cardiovascular/cerebrovascular diseases or malignant tumors.
- ii) Subjects with diseases which may affect bone metabolism or calcium absorption, such as serious malabsorption syndrome, enteritidis, hyperparathyroidism, chronic infectious arthritis, osteomalacia and diabetes.
- iii) Subjects receiving medications such as glucocorticoid, estrogen, androgen, calcitonin, and antidiabetic agents.
- iv) The diagnosis of osteopenia and osteoporosis was not clear.
- v) The data were incomplete or could not be obtained by conversion.
- vi) The study was a review, case report, commentary, or animal/cell-based.

## 2.4 Literature screening

Two researchers independently screened the literature according to the inclusion and exclusion criteria and then compared their findings with each other. First, duplicate studies, animal/cell experiments, case reports, and commentaries were removed. Second, the studies were screened based on their title and abstract. Last, the full text was read to decide whether the study should be included. If there were objections, the studies were discussed with a third party to decide whether to include them.

## 2.5 Information extraction

We read the full text of each study and extracted the relevant information, which included the name of the first author, publication year, country the studied was performed in, the average age of subjects, the sex of patients and lipid-lowering drugs. In addition, the occurrence of osteopenia or OP, and the differences in blood lipid levels between different groups were extracted.

## 2.6 Quality assessment

The quality of the literature included was evaluated according to the Newcastle-Ottawa Scale (NOS) form. A score of 1–3 points was considered poor quality, 4–6 points indicated moderate quality, and a score of 7–9 points was considered high quality. The specific scoring criteria were as follows: Selection (adequate case definition, case representativeness, selection of controls, definition of controls), Comparability (comparability of cases and controls based on the design or analysis), and Exposure (ascertainment of exposure, same method of ascertainment for cases and controls, non-response rate) (**Supplementary material 2**).

## 2.7 Statistical analysis

The meta-analysis was performed using Revman 5.3 and Stata 13.0 software. All blood lipid indicators were considered continuous variables, and the effect amount was shown as the mean difference (MD) and 95% confidence interval (95%CI). An inverse variance model was used as the statistical model. Heterogeneity analysis was performed by Q and  $I^2$  tests. If  $P > 0.1$  in the Q test or  $I^2 < 50\%$  in the  $I^2$  test, it was considered homogeneous. If  $P < 0.1$  or  $I^2 > 50\%$ , it was regarded as heterogeneous, and the source of heterogeneity was identified. If the heterogeneity was large, a random effects model was used, whereas if the heterogeneity was small, a fixed effects model was used. Subgroup analysis was also used to identify the source of heterogeneity. It was based on subject characteristics (postmenopausal women, unclassified women, men or adults) and lipid-lowering drugs (taking or not taking) to do subgroup meta-analysis. If the heterogeneity was significantly reduced, the characteristics were the source of heterogeneity. Of note, if there was only one study in one subgroup, the result was not listed. Egger's test was conducted using Stata software to quantitatively evaluate publication bias. If  $P > 0.05$ , publication bias was considered non-existent.

## 3 Results

### 3.1 Literature search results and basic characteristics of the included literature

We retrieved 6,680, 11,899, and 2,476 articles from PubMed, Embase, and Cochrane libraries, respectively. Therefore, a total of 21,055 articles were imported into Endnote to manage the references. A stepwise screening was performed according to a previous method (**Fig. S1**). A total of 12 studies were finally included that involved 12,395 subjects. Among them, there were 8 osteopenia studies and 12 osteoporosis studies. The basic characteristics of included studies were shown in **Table**.

First author	Year	Country	Age	Sex	Subjects	Sample size	NOS score	Lipid-lowering drugs	Event	
									Osteopenia	OP
Alay <sup>[9]</sup>	2020	Turkey	53.9±6.7	F	Postmenopausal	452	6	√	√	√
Aleksandar <sup>[10]</sup>	2012	Serbia	57.0±4.8	F	Postmenopausal	300	6	√	√	√
Arikan <sup>[11]</sup>	2011	Turkey	54.7±8.8	F	Postmenopausal	107	7	√	√	√
Bijelic <sup>[13]</sup>	2016	Herzegovina	About 63	F	Postmenopausal	200	7			√
Gu <sup>[6]</sup> (1)	2019	China	53.5±9.0	M	Men	2,830	7	√	√	√
Gu (2)	2019	China	52.3±8.9	F	Unclassified women	5,754	7			
Han <sup>[19]</sup>	2017	China	59.9±11.0	M, F	Adults	674	8	√	√	√
Huang <sup>[20]</sup>	2016	China	60.6±11.9	F	Postmenopausal	233	7	√	√	√
Li <sup>[8]</sup>	2015	China	62.3±6.2	F	Postmenopausal	790	6			√
Pliatsika <sup>[27]</sup>	2012	Greece	53.0±5.7	F	Postmenopausal	591	6	√	√	√
Qi <sup>[29]</sup>	2016	China	56.6±4.9	F	Postmenopausal	260	7	√	√	√
Sivas <sup>[31]</sup>	2009	Turkey	60.0±6.0	F	Postmenopausal	107	6			√
Verit <sup>[34]</sup>	2007	Turkey	54.0±3.6	F	Postmenopausal	97	6			

Footnote: M, male; F, female; OP, osteoporosis.

Table

Basic characteristics of included studies.

## 3.2 Quality assessment

According to the NOS form, we systematically evaluated the quality of the included articles. Six articles scored 6 points, 5 articles scored 7 points, and 1 article scored 8 points. Overall, the quality of the included literature was acceptable.

## 3.3 Lipid levels in patients with osteopenia

### 3.3.1 TC

There were 8 studies (9,747 subjects) that measured TC levels in patients with osteopenia. Using a random effects model, the total effect amount was MD = 0.08 mmol/L (95%CI: -0.06, 0.22;  $I^2 = 87\%$ ;  $P < 0.00001$ ), which indicated large heterogeneity (Fig. 1A). A subgroup analysis was performed according to the characteristics of the subjects: the postmenopausal women subgroup had a MD = 0.05 mmol/L (95%CI: -0.25, 0.36;  $I^2 = 87\%$ ; and  $P < 0.00001$ ) (Fig. 1B). Another subgroup analysis based on the lipid-lowering drugs: no lipid-lowering drugs subgroup had a MD = 0.11 mmol/L (95%CI: -0.03, 0.25;  $I^2 = 21\%$ ;  $P = 0.36$ ); the other subgroup had a MD = 0.08 mmol/L (95%CI: -0.12, 0.27;  $I^2 = 91\%$ ;  $P < 0.00001$ ) (Fig. 1C). The results indicated that there was no difference in TC levels between the osteopenia group and the normal group in subjects without taking drugs. There was no publication bias because  $P = 0.969$ , according to Egger's test (Fig.S2A).

### 3.3.2 TG

There were 7 studies (9,471 subjects) that measured TG levels in patients with osteopenia. Using a random effects model, the MD = 0.04 mmol/L (95%CI: -0.05, 0.12;  $I^2 = 68\%$ ;  $P = 0.003$ ), which indicated large heterogeneity (Fig. 2A). Subgroup analyses were then performed. The postmenopausal women subgroup had a MD = 0.00 mmol/L (95%CI: -0.18, 0.19;  $I^2 = 81\%$ ;  $P = 0.0001$ ) (Fig. 2B). The no lipid lowering drugs subgroup had a MD = -0.01 mmol/L (95%CI: -0.09, 0.07;  $I^2 = 6\%$ ;  $P = 0.34$ ), the other subgroup had a MD =

0.07 mmol/L (95%CI: 0.03,0.12;  $I^2 = 76\%$ ;  $P = 0.002$ ) (Fig. 2C). Therefore, no difference in TG levels existed between the osteopenia group and the control group in subjects without taking lipid-lowering drugs.  $P = 0.817$  in Egger's test, which indicated that there was no publication bias (Fig. S2B).

### 3.3.3 HDL-C

A total of 6 studies (9,360 subjects) measured HDL-C levels in patients with osteopenia. The total effect amount was MD = 0.01 mmol/L (95%CI: -0.01,0.02;  $I^2 = 38\%$ ;  $P = 0.14$ ) in the fixed effects model (Fig. 3). There was no difference in HDL-C levels between the osteopenia group and the control group. We found that  $P = 0.734$  in Egger's test, indicating that there was no publication bias (Fig. S2C).

### 3.3.4 LDL-C

Six studies (9,420 subjects) determined LDL-C levels in patients with osteopenia. A random effects model was used, and the MD = 0.04 mmol/L (95%CI: -0.03, 0.12;  $I^2 = 66\%$ ;  $P = 0.007$ ) (Fig. 4A). Subgroup analyses were performed to identify the source of heterogeneity. In the postmenopausal women subgroup, the MD = 0.02 mmol/L (95%CI: -0.09, 0.13;  $I^2 = 0\%$ ;  $P = 0.74$ ) (Fig. 4B). In subjects without lipid-lowering drugs, the MD = 0.10 mmol/L (95%CI: 0.00, 0.19;  $I^2 = 0\%$ ;  $P = 0.74$ ); In subjects who were taking drugs, the MD = 0.01 mmol/L (95%CI: -0.10, 0.12;  $I^2 = 81\%$ ;  $P = 0.001$ ) (Fig. 4C). There was no difference in LDL-C levels between the two groups in postmenopausal women or subjects without lipid-lowering drugs. There was no publication bias because  $P = 0.639$  in Egger's test (Fig. S2D).

## 3.4 Lipid levels in patients with osteoporosis

### 3.4.1 TC

A total of 12 studies (7,870 subjects) measured TC levels in patients with osteoporosis. Using a random effects model, the MD was 0.20 mmol/L (95%CI: -0.04,0.43;  $I^2 = 94\%$ ;  $P < 0.00001$ ), indicating large heterogeneity (Fig. S3A). A subgroup analysis was performed according to the characteristics of the subjects: postmenopausal women had a MD = 0.18 mmol/L (95%CI: -0.19, 0.56;  $I^2 = 95\%$ ;  $P < 0.00001$ ) (Fig. S3B). The other subgroup analysis was performed based on whether or not taking lipid-lowering drugs. Subjects who were not taking lipid-lowering drugs had a MD = 0.20 mmol/L (95%CI: -0.11, 0.41;  $I^2 = 79\%$ ;  $P < 0.00001$ ), In others, the MD = 0.18 mmol/L (95%CI: -0.29, 0.65;  $I^2 = 97\%$ ;  $P < 0.00001$ ) (Fig. S3C). The results showed neither characteristics of the subjects or lipid-lowering drugs was not the source of heterogeneity. There was no publication bias because  $P = 0.731$  in Egger's test (Fig. S4A).

### 3.4.2 TG

Eleven articles involving 7,597 subjects reported TG levels in patients with osteoporosis. The total effect amount was MD = 0.02 mmol/L (95%CI: -0.10, 0.14;  $I^2 = 79\%$ ;  $P < 0.00001$ ) in a random effects model, which indicated large heterogeneity (Fig. 5A). The postmenopausal women subgroup had a MD = 0.01 mmol/L (95%CI: -0.18, 0.11;  $I^2 = 83\%$ ;  $P < 0.00001$ ) (Fig. 5B). The subjects without taking lipid-lowering drugs subgroup had a MD = -0.04 mmol/L (95%CI: -0.14,0.07;  $I^2 = 49\%$ ;  $P = 0.07$ ); In the other subgroup, the MD = 0.10 mmol/L (95%CI: -0.14,0.33;  $I^2 = 88\%$ ;  $P < 0.00001$ ) (Fig. 5C). There was no difference in TG between the two groups in subjects who were not taking lipid-lowering drugs. We found that  $P = 0.657$  in Egger's test, suggesting that there was no publication bias (Fig. S4B).

### 3.4.3 HDL-C

Ten studies involving 7,424 subjects measured HDL-C levels in patients with osteoporosis. The MD was 0.05 mmol/L (95%CI: 0.03, 0.07;  $I^2 = 31\%$ ;  $P = 0.15$ ) in the fixed effect model, which indicated that HDL-C levels were higher in the osteoporosis group than in the control group (Fig. 6).  $P = 0.627$  in Egger's test, which indicated that there was some publication bias (Fig. S4C).

### 3.4.4 LDL-C

A total of 10 studies (7,512 subjects) reported LDL-C levels in patients with osteoporosis. The total effect amount was MD = 0.23 mmol/L (95%CI: 0.07,0.39;  $I^2 = 89\%$ ; and  $P < 0.00001$ ), indicating large heterogeneity (Fig. S5A). Therefore, subgroup analyses were performed. Postmenopausal women had a MD = 0.29 mmol/L (95%CI: -0.02,0.59;  $I^2 = 91\%$ ;  $P < 0.00001$ ) based the characteristics of the subjects (Fig. S5B). Subjects who did not took lipid-lowering drugs had a MD = 0.16 mmol/L (95%CI: 0.02,0.31;  $I^2 = 68\%$ ;  $P = 0.005$ ). In

subjects who took drugs, the MD = 0.35 mmol/L (95%CI: -0.04, 0.73;  $I^2 = 96\%$ ;  $P < 0.00001$ ) (Fig. S5C). So the heterogeneity was not found.  $P = 0.452$  in Egger's test, indicating that there was no publication bias (Fig. S4D).

## 4 Discussion

We used the Egger's test to quantitatively evaluate publication bias. All P-values were  $> 0.05$ , indicating that there was no publication bias. The quality of the included literature was evaluated by the NOS score, which were all above median level, indicating that the quality of the included literature was acceptable, and the results of the meta-analysis were relatively credible.

This meta-analysis involved 12 studies and a total of 12,395 subjects. The studies included two events (osteopenia and OP) and four indicators (TC, TG, HDL-C, and LDL-C). The larger number of subjects strived for a stable result. Some results in this meta-analysis were heterogeneous, so we performed subgroup analyses based on two factors. The first factor was the characteristics of the subjects, which may be due to the actions of hormone. Postmenopausal women are more prone to OP because of lack of estrogen protection. The other factor was whether or not take lipid-lowering drugs, because it affects blood lipid levels. Even if subgroup analyses were conducted, some sources of heterogeneity were still not found, and we considered the possible reason was mixed effects of multiple confounding factors.

Trimpou et al.<sup>[33]</sup> observed the necrosis of the femoral head under an electron microscope and found that the number and size of fat cells were significantly increased, suggesting that hypercholesterolemia is an independent risk factor for osteoporotic fractures. A recent meta-analysis, including 33 studies (16 cohort studies, 7 case-control studies, and 10 randomized controlled trials) showed that statins reduced the risk of total and hip fractures. The use of statins has been associated with an increase in total hip BMD and lumbar spine and was found to increase the expression of bone formation markers, such as osteocalcin<sup>[42]</sup>.

The pathophysiological relationship between blood lipid levels and BMD remains unclear. Most studies report that eating a high-fat diet reduces bone strength, changes the microstructure of the cancellous bone compartment, and changes the bone marrow environment, and low-level inflammation may play a role in these processes<sup>[43]</sup>. TC and its metabolites have been reported to affect the functional activity of osteoblasts *in vitro* and *in vivo*<sup>[44]</sup>. Elevated serum lipids may cause bone blood vessels to accumulate in the subendothelial matrix and may inhibit the differentiation and mineralization of bone cells.

This study has some limitations. First, the overall heterogeneity of the meta-analysis results obtained in this study was large, and the source of heterogeneity according to subject characteristics or lipid-lowering drugs was not identified in some studies. Considering the number of included studies, the sources of heterogeneity may involve many aspects. Second, most of the participants included in this meta-analysis were postmenopausal women because there are limited studies on men. However, the male population is a group that needs our attention. We look forward to more individual studies on male OP to perform a future meta-analysis. Third, we included case-control studies with weaker levels of evidence. Long-term cohort studies are needed to determine the effects of elevated blood lipids on osteopenia, OP, and fractures.

## 5 Conclusions

In conclusion, there was no difference of TC, TG and LDL-C between osteopenia/OP group and control group in subjects who were not taking lipid-lowering drugs. HDL-C was elevated in OP group but not in osteopenia group in all subjects. In addition, no difference existed between osteopenia and control group in postmenopausal women. It reminds us that blood lipid levels should be controlled and maintained in an appropriate range to reduce the risk of osteopenia, or OP. In future, blood lipid levels can be grouped and incidence of osteopenia and OP could be obtained after long follow up, so results would be more powerful.

## Abbreviations

BMD: bone mineral density, BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, MD: mean difference, TC: total cholesterol, TG: triglyceride, OP: osteoporosis, 95%CI: 95% confidence interval.

## Declarations

## Ethics approval and consent to participate

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

## Consent for publication

Not applicable.

## Availability of data and materials

The original data can be obtained by email request.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' Contributions

ZH: Conceptualization, Methodology, Writing - original draft. SA, LY, QLC and ZC: Methodology, Software. SGY and RLP: Conceptualization, Writing - review & editing. All authors read and approved the final manuscript.

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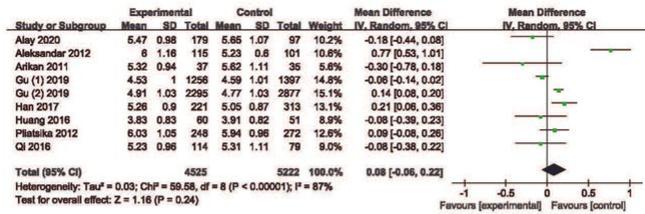
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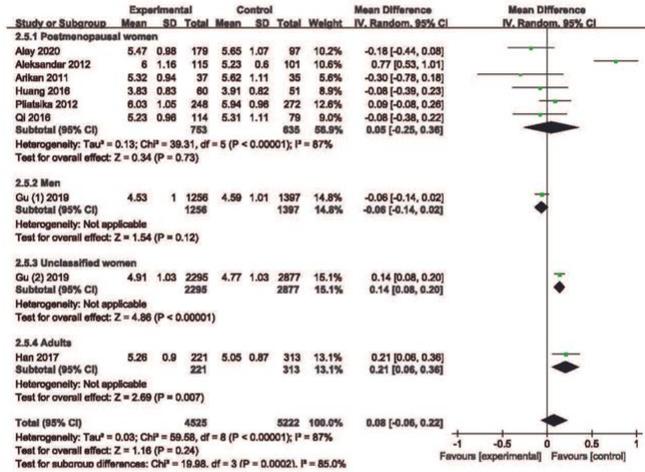
## Figures

Fig 1

A



B



C

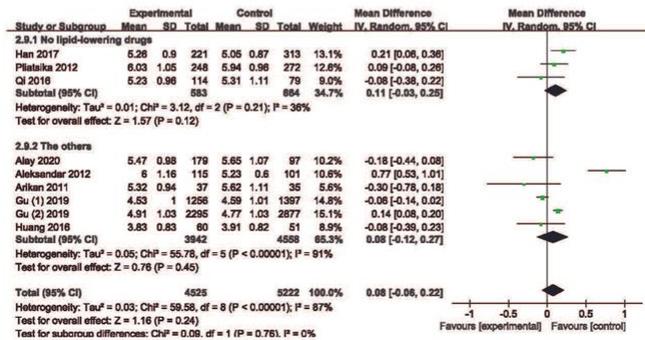
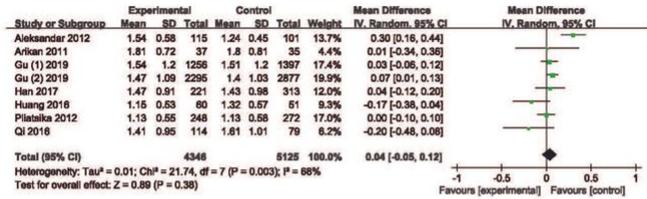


Figure 1

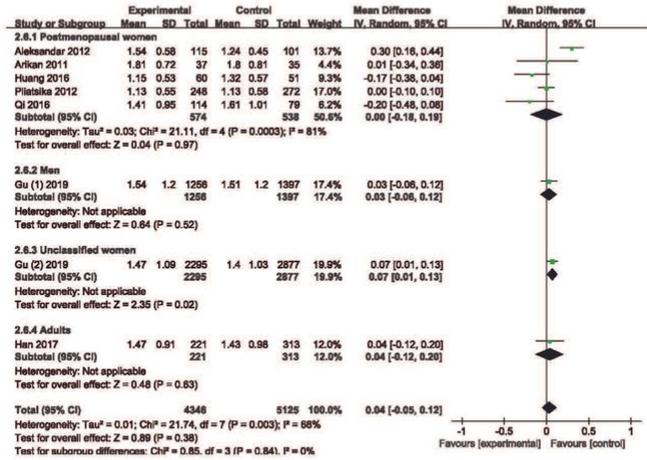
Forest plot comparing the total cholesterol level of the control and osteopenia groups. (A) total subjects; (B) subgroup analysis based on subjects' characteristics; (C) subgroup analysis based on lipid-lowering drugs.

Fig 2

A



B



C

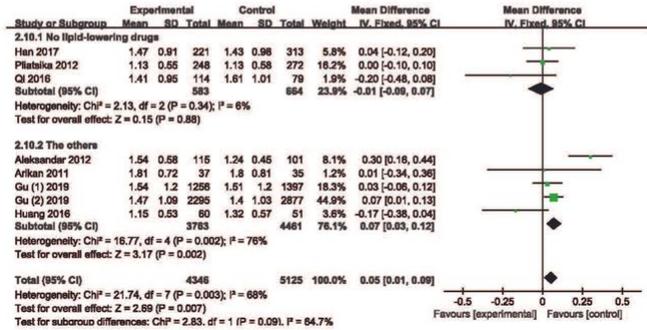


Figure 2

Forest plot comparing the triglyceride level of the control and osteopenia groups. (A) total subjects; (B) subgroup analysis based on subjects' characteristics; (C) subgroup analysis based on lipid-lowering drugs.

Fig 3

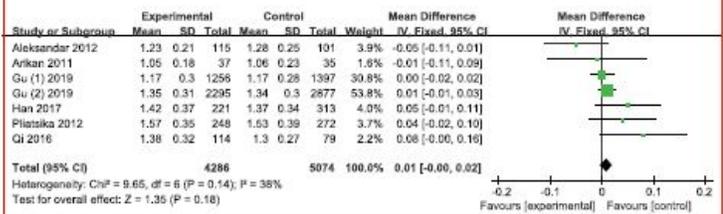
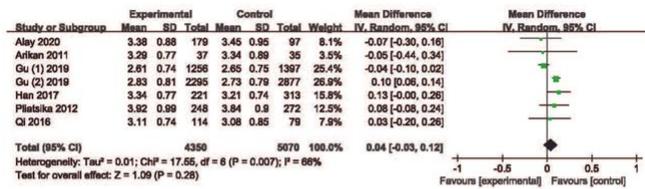


Figure 3

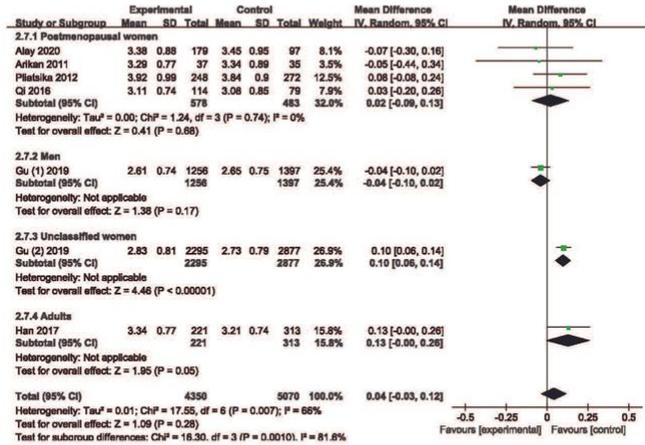
Forest plot comparing the high-density lipoprotein cholesterol level of the control and osteopenia groups.

Fig 4

A



B



C

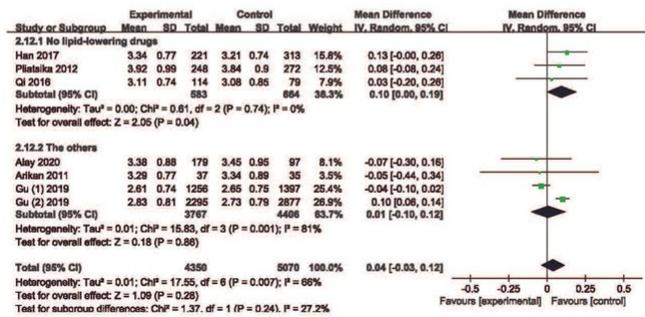


Figure 4

Forest plot comparing the low-density lipoprotein cholesterol level of the control and osteopenia groups. (A) total subjects; (B) subgroup analysis based on subjects' characteristics; (C) subgroup analysis based on lipid-lowering drugs.

Fig 5

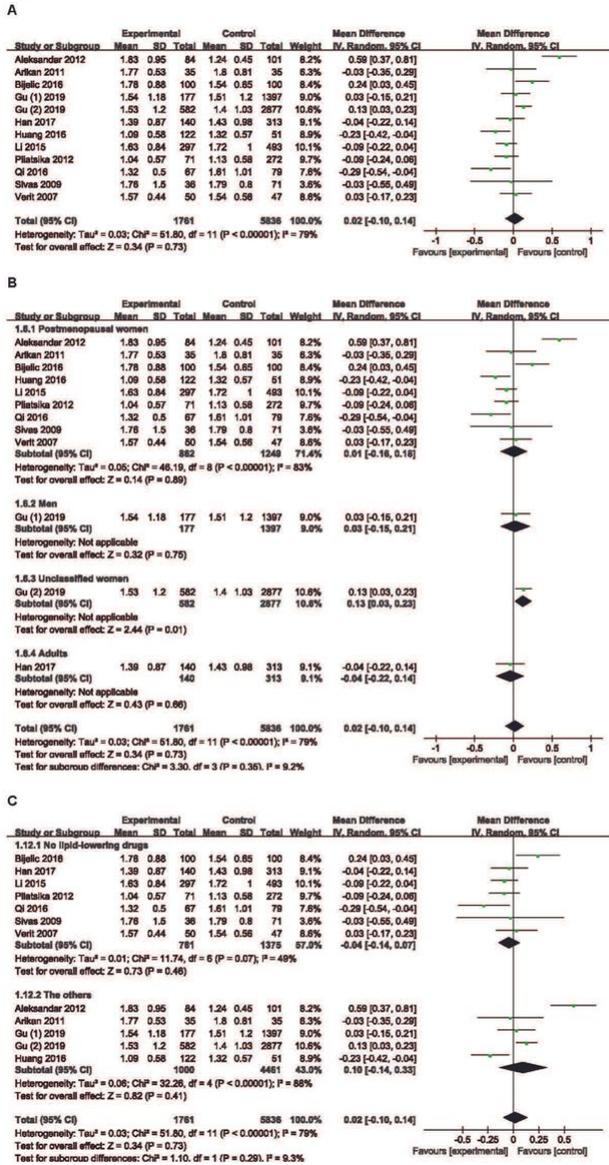


Figure 5

Forest plot comparing the triglyceride level of the control and osteoporosis groups. (A) total subjects; (B) subgroup analysis based on subjects' characteristics; (C) subgroup analysis based on lipid-lowering drugs.

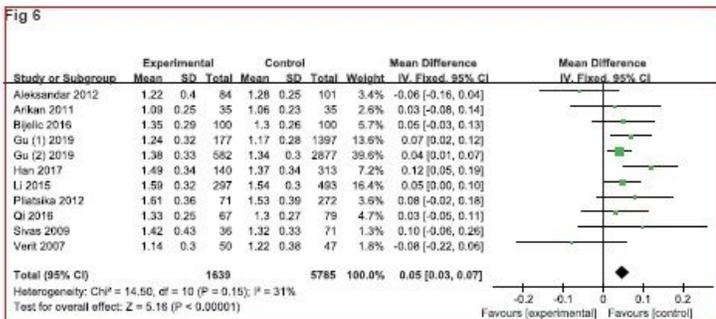


Figure 6

Forest plot comparing the high-density lipoprotein cholesterol level of the control and osteoporosis groups.

## Supplementary Files

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