Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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REVIEW

Relationship between nonalcoholic fatty liver disease and bone mineral density in adolescents with obesity: a meta-analysis

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Purpose: Many studies have reported the relationship between nonalcoholic fatty liver disease (NAFLD) and bone mineral density (BMD) among adults. However, fewer studies on this topic have been reported in adolescents. We thus conducted a meta-analysis to show the association between NAFLD and BMD in adolescents with obesity.

Materials and methods: Computer retrieval was carried out via PubMed, Embase, Cochrane Library and the Cochrane Central Register of Controlled Trials from inception to September 2018. Six published case–control studies that assessed the relationship between NAFLD and BMD were included.

Results: The six studies included 217 obese adolescents with NAFLD and 236 controls. The meta-analysis indicated that obese children with NAFLD had a lower BMD and *Z*-score than the control group (weighted mean difference [WMD]–0.03, 95% CI [−0.05, –0.02], *P*=0.000; [WMD] –0.26, 95% CI [−0.37, –0.14], *P*=0.000). However, we analyzed the factor of bone mineral content, and there was no correlation between the two groups ([WMD]–55.99, 95% CI [−132.16, 20.18], *P*=0.150).

Conclusion: Obese children with NAFLD are more susceptible to osteoporosis than children with only obesity. Because of the limitations related to the quantity and quality of the included literature, further studies are still needed.

Keywords: nonalcoholic fatty liver disease, NAFLD, bone mineral density, BMD, meta-analysis, obesity, adolescent

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world. Nearly 25.24% of the overall population has NAFLD.[1,2] Moreover, NAFLD is the principal cause of chronic liver disease in children, especially among overweight and obese individuals in industrialized countries.[3] On a clinical spectrum, NAFLD ranges from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH) and liver cirrhosis and fibrosis.[4] The serious outcomes of NAFLD are hepatocellular carcinoma and liver failure.[5] Unfortunately, in addition to liver destruction, the effects of NAFLD can also occur in extra hepatic organs and cause type 2 diabetes and cardiovascular disease.[6,7]

It is well established that the affecting mechanisms of NAFLD are insulin resistance (IR) and chronic inflammation.[8] Additionally, a high-calorie diet and a sedentary lifestyle contribute to NAFLD development.[9] The incidence rate of NAFLD is coincident with the increase in obesity.[10] Therefore, NAFLD has attracted worldwide attention.

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Osteoporosis is a group of bone diseases with various causes, including general factors related to aging, obesity and sex steroid deficiency, as well as specific risk factors such as the use of glucocorticoids, reduced bone quality, and disruption of microarchitectural integrity.[11] In most cases of osteoporosis, the reduction in bone tissue is mainly due to increased bone resorption. Osteoporosis is characterized by low bone mineral density (BMD), bone pain and easy fracture.[12] Osteoporosis is a silent disease until fractures occur with increasing frequency, which can cause important problems and even death.[13] In industrialized countries, 9%–38% of women and 1%–8% of men >50 years suffer from osteoporosis.[14] Therefore, osteoporosis is not only harmful to health but also increases the financial burden of the impacted countries.[15]

An epidemiological study from Portugal showed that ~3% of adolescents are obese, and 30% are overweight.[16,17] In 2017, the Health Behaviour in School-Aged Children from the WHO showed that, among more than half of the European countries, the incidence of adolescent obesity rapidly increased from 2002 to 2014.[18] Many studies have demonstrated that NAFLD is associated with low BMD and osteoporosis,[19–21] but most studies have focused on adults, and surveys targeting children and adolescents have been limited.[22] Here, we investigated the relationship between NAFLD and BMD in adolescents with obesity through a meta-analysis.

Materials and methods

Research strategy

This meta-analysis was conducted and reported following the PRISMA guidelines.[23] All the included studies were filtered through PubMed, Embase, and the Cochrane Database from inception to September 2018. We used the following keywords and terms: ("Non-alcoholic Fatty Liver Disease," "Non alcoholic Fatty Liver Disease," "NAFLD," "Nonalcoholic Fatty Liver Disease," "Fatty Liver, Nonalcoholic," "Nonalcoholic Fatty Livers," "Steatohepatitis, Nonalcoholic") and ("Bone Density," "Bone Densities," "Density, Bone," "Bone Mineral Density," "Bone Mineral Content").

Inclusion criteria

Inclusion factors were: 1) study types including prospective cohort, retrospective cohort, case–control, and cross-sectional studies evaluating the association between NAFLD and BMD; 2) all the participants were adolescents from puberty stage I to V;[24] 3) NAFLD patients were diagnosed with an ultrasound examination or pathological examination to make a clear and definite diagnosis, and all the participants were obese according to body mass index (BMI); and 4) BMD was measured by dual energy X-ray absorptiometry.

Exclusion criteria

Exclusion factors were 1) other diseases that could cause NAFLD were excluded, such as viral infections, alcohol intake, and the use of drugs and 2) none of the subjects followed specific diets or therapeutic treatments that could influence BMD or liver function.

Data collection

Two investigators abstracted the data from the suitable studies and conformed them to the same criteria, including research topics, the details of the first author, year of publication, study type, number of patients and number in the control group, basic characteristics of participants, and mean values and SDs of BMD.

Quality assessment

The Newcastle Ottawa Scale (NOS) was used to assess the quality of the involved studies.[25] Studies with a score of 7–9 points were considered to be of high quality. The score of each study is represented in Table 1.

Statistical analysis

Stata Statistical Software (ver. 12.0; StataCorp LP, College Station, TX, USA) was utilized in the meta-analysis, and $P<0.05$ was regarded as statistically significant. Continuous variables are presented as weighted mean differences (WMDs). If I^2 was more than 50%, heterogeneity was recognized as significant.[26] When the heterogeneity was high, a random effects model was used to evaluate the relationship between the two groups. If no obvious heterogeneity existed in the research results, a fixed effects model was used for the meta-analysis.[27,28]

Results

Literature selection

A total of 116 studies were selected from the databases mentioned at the beginning. After eliminating 32 duplicated studies and screening the titles and abstracts for studies that were not relevant because of the topic or research type, 8 studies were included in the full-text review. Finally, there were six studies included in our meta-analysis. A total of 217 obese adolescents with NAFLD and 236 obese adolescents

Table 1 Main characteristics of included studies and quality assessment score

Author	Year	Region	Study type	Diagnosis	Number		Age (y)		BMI (kg/m^2)		BMD (g/cm^2)		BMC (g)		Z-score		NOS
					Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	
Pacifico et al[57]	2013	Italy	Case–control	MRI	44	44	12.5±1.8	12.5±1.8	NA	NA	NA	NA	NA	NA	1.55±1.02	1.95±0.71	8
Labayen et al[58]	2018	Spain	Case–control	MRI	41	74	10.5±1.1	10.6±1.1	26.2±3.3	25.0±3.2	0.89±0.05	0.93±0.06	1308±196	1369±246	0.94±1.07	1.39±0.94	9
Moscal et al[59]	2018	Italy	Case–control	Ultrasound liver biopsy	25	9	12.6±2.6	13.2±3.2	28.0±4.3	28.2±3.6	0.87±0.06	0.97±0.12	1740.7± 459	1714.3± 370	0.8±1.0	1.4±1.2	8
Campos et al[60]	2012	Brazil	Case–control	Ultrasound	18	22	NA	NA	39.9 ± 5.1	35.8 ± 5.3	1.2±0.1	1.2±0.1	2767.0± 498.3	2835.6± 371.2	1.5±1.0	1.6±1.0	8
Pirgon et al[61]	2011	Turkey	Case–control	Ultrasound	42	40	12.5±1.87	12.1±1.34	NA	NA	1.03±0.14	1.03±0.1	NA	NA	0.56±0.3	1.02±0.9	8
Chang et al[62]	2015	Korea	Case–control	Ultrasound	47	47	11.5±2.6	9.60±3.20	25.6±4.3	25.1±3.8	1.0±0.28	0.94±0.11	NA	NA	0.6±0.43	0.74±0.29	6

Notes: [a]Site of BMD measurement in this study was whole body. [b]Sites of BMD measurement in this study were lumbar spine (L1–L4). Data are presented as mean±SD where applicable.
Abbreviations: BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; NA, not applicable; NOS, Newcastle-Ottawa Scale.

were included, and the retrieved procedures and excluded details can be found in Figure 1.

Characteristics of the included studies

The basic characteristics of the six included studies are shown in Table 1. Obese adolescents with NAFLD were included in the case group, whereas obese children without NAFLD were included in the control group. The total number of patients in the case group was 217, whereas the control group included 236 individuals. By scanning the full texts of the six studies, we found that the study types were case–control. Among the included studies, five studies were performed in Europe, and one was performed in Asia. Ultrasound, MRI, and liver biopsy were used to diagnose NAFLD. In addition, the study performed in Asia had three groups: the control group, the simple steatosis group, and the NASH group. We integrated the first two groups into one, which was regarded as the control group in this meta-analysis. The NASH group was included in the case group. In addition, five studies had a high quality score, and the one study conducted in Asia had a lower score.

Results of the meta-analysis

Contrast indicator of BMD (g/cm^2)

A total of 173 cases and 192 controls were included. A meta-analysis was conducted using a fixed effects model to evaluate the correlation between the case group and the control group with respect to BMD. The results showed that I^2=60.2%, P=0.039 (Figure 2A). Because of significant heterogeneity, we used a random effects model; however, the outcome was the same as that of the above-mentioned model (Figure 2B). After eliminating the study with a low quality score, we performed the analysis using the fixed effects model again, and the result was I^2=46.2%, P=0.000 (Figure 3). The meta-analysis indicated that obese adolescents with NAFLD had a higher BMD than those without the illness.

Assessing differences using Z-scores

In this section, six studies were included in the meta-analysis. There were 217 patients in the case group and 236 individuals in the control group. A fixed effects model was used to assess the Z-score relationship between the two groups. The results demonstrated that I^2=26.9%, P=0.000 (Figure 4).

The meta-analysis showed that obese adolescents had a positive Z-score; therefore, the Z-scores revealed that obese adolescents with NAFLD were more likely to develop osteoporosis.

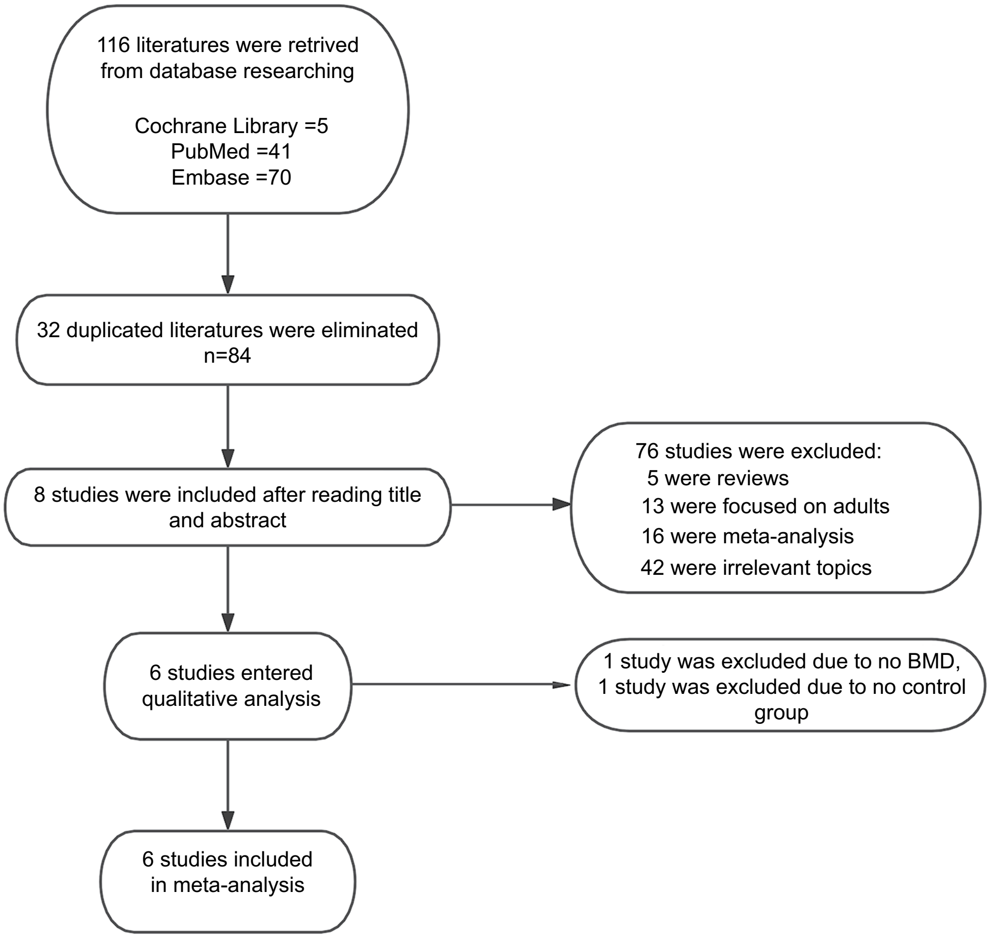

Figure 1 Flowchart of the studies' selecting process and results.
Abbreviation: BMD, bone mineral density.

Assessing differences using BMC (g)

Three studies contained indicators of BMC. The total number in the case group was 84, whereas in the control group the number was 105. Through a meta-analysis, a fixed effects model showed that there was no significant difference between the NAFLD group and non-NAFLD group (I^2=0.0%, P=0.150). The outcome is shown in Figure 5.

Discussion

According to this meta-analysis, we can conclude that obese adolescents with NAFLD have a higher BMD and *Z*-score than obese adolescents without NAFLD. However, when comparing the BMCs of the two groups, there was no difference. This is the only study to our knowledge to investigate the relationship between BMD and NAFLD in adolescents.

A recent study from Handzlik-Orlik et al[29] showed a relationship between NAFLD and osteoporosis. In addition, a retrospective study from People's Republic of China that involved more than 7,000 men demonstrated that men with NAFLD had a high risk of suffering from an osteoporotic fracture.[30] A reduced BMD may be attributed to liver disorder.[31,32] Although some clinical studies provided evidence that NAFLD is related to low BMD,[19–34] the pathogenesis underlying the correlation between NAFLD and decreased BMD is not clear.

According to current studies, several hypotheses have been proposed, including mechanisms involving tumor necrosis factor (TNF)-α, osteopontin (OPN), osteoprotegerin (OPG), osteocalcin and fetuin-A.[35–42] The main factor out of these is TNF-α. A previous study demonstrated that TNF-α could enhance osteoclast activity, inhibit osteoblast differentiation, and increase osteoblastapoptosis.[43–45] Additionally, vitamin D plays a significant role in liver pathophysiology and NAFLD.[46] These cytokines and regulatory pathways have been associated with the presence of NAFLD.[47] Therefore, it has been proposed that the presence of systematic and constant inflammation in NAFLD patients contributes to the correlation between NAFLD and low BMD.[45] When focusing on children and adolescents, apart from the mechanisms mentioned above, a study of Hispanic children indicated

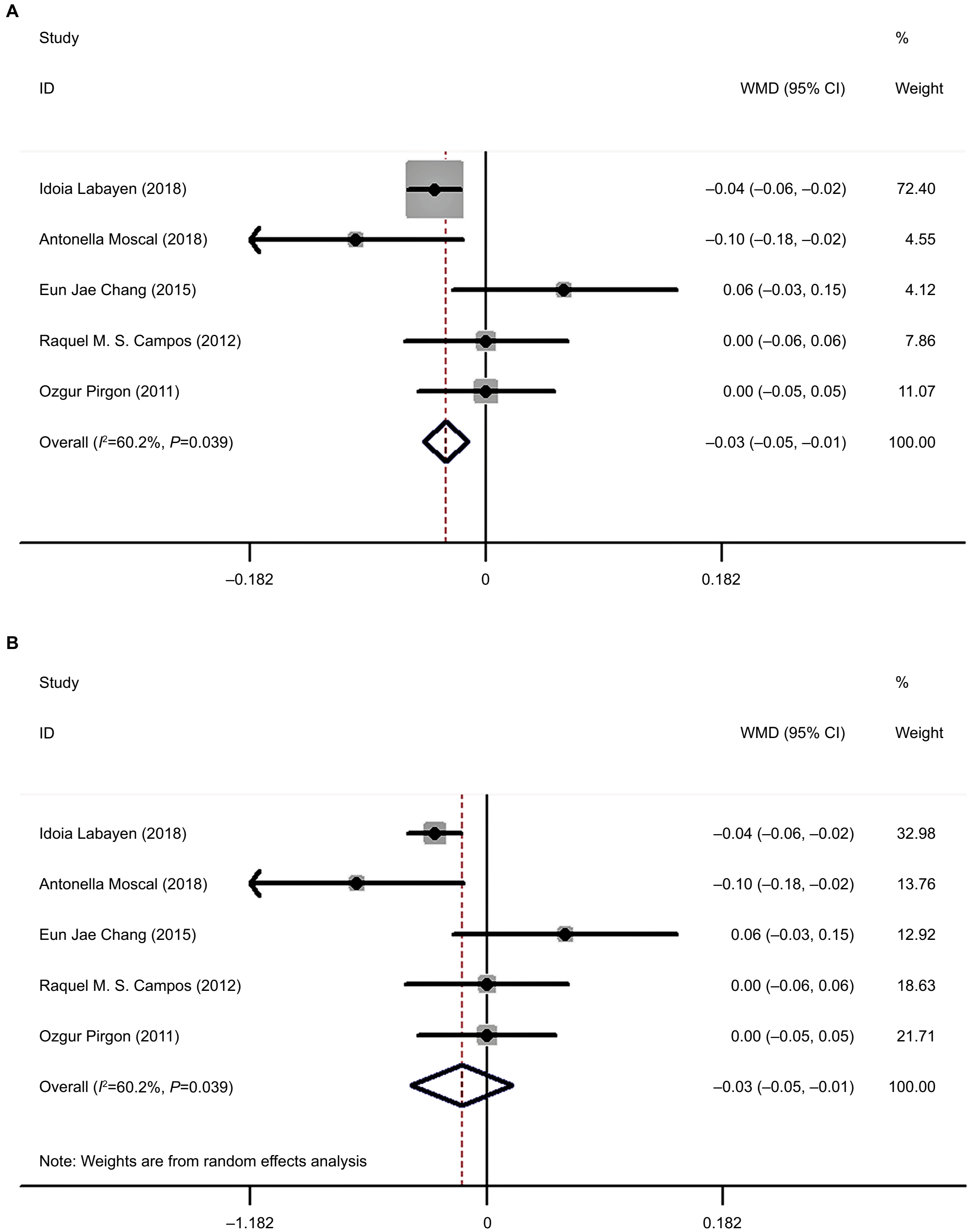

Figure 2 (**A**) Meta-analysis of the correlation between obese adolescents with NAFLD and obese adolescents without NAFLD in BMD (fixed effects model). (**B**) Meta-analysis of the correlation between obese adolescents with NAFLD and obese adolescents without NAFLD in BMD (random effects model).
Abbreviations: BMD, bone mineral density; NAFLD, nonalcoholic fatty liver disease; WMD, weighted mean difference.

that NAFLD was associated with obesity and the PNPLA3 gene.[48] NAFLD is strongly associated with obesity.[49] Childhood obesity can develop into adult obesity.[50,51] Simmonds et al[52] conducted a meta-analysis, and the results showed that obese children had a 5-fold higher risk of adult obesity than normal-weight children. Therefore, children and adolescents who are overweight and obese are susceptible to NAFLD and problems related to bone metabolism.

Boys had notably higher BMC values than girls older than 14 years old; however, before this age cutoff, there

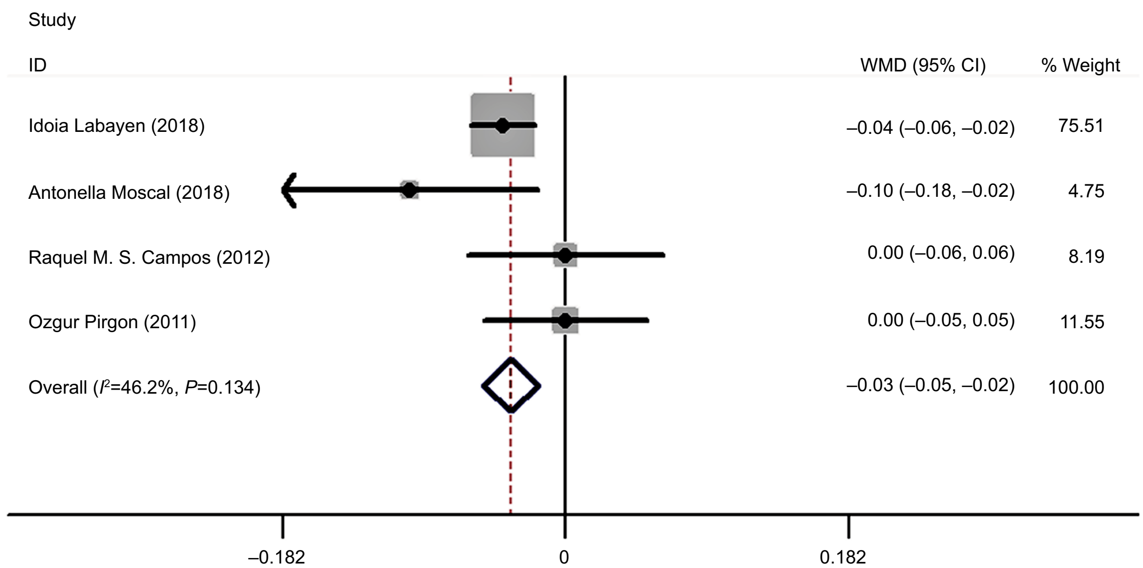

Figure 3 After eliminating the low score study the graph shows the meta-analysis of the correlation between obese adolescents without NAFLD in BMD (Fixed effects model).
Abbreviations: BMD, bone mineral density; NAFLD, nonalcoholic fatty liver disease; WMD, weighted mean difference.

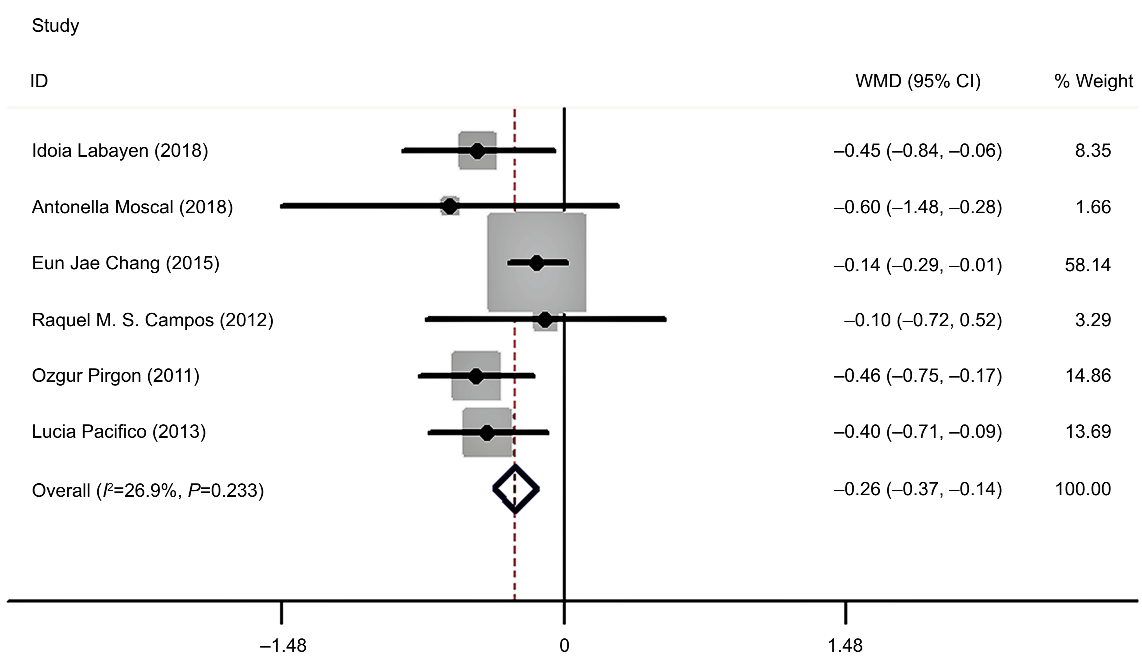

Figure 4 Meta-analysis of the correlation between obese adolescents with NAFLD and obese adolescents without NAFLD in *Z*-score (Fixed effects model).
Abbreviation: NAFLD, nonalcoholic fatty liver disease; WMD, weighted mean difference.

were no sex differences in total body, femoral neck or lumbar spine BMD in a study conducted by Baxter-Jones et al.[53] Other experts also demonstrated that within the age range of 9–11, no differences in total BMD were observed between boys and girls.[54,55] As for adolescents with NAFLD, research on the prevalence of osteoporosis in different genders is limited. Yu et al[56] performed a study on the relationship between bone marrow fat content and hepatic fat content in children with NAFLD. In their study, they found that in boys, bone marrow fat content and hepatic

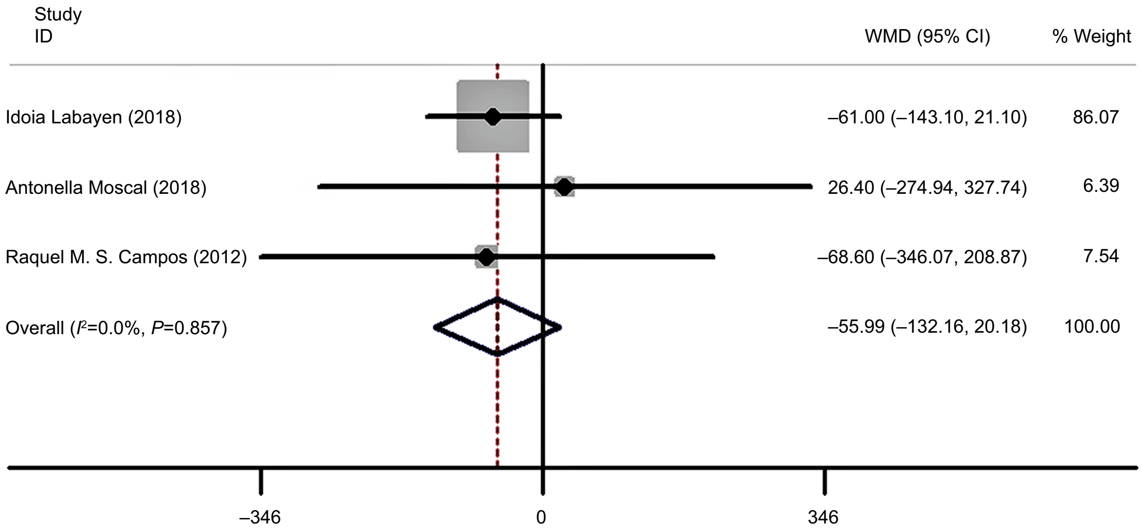

Figure 5 Meta-analysis of the correlation between obese adolescents with NAFLD and obese adolescents without NAFLD in BMC (Fixed effects model).
Abbreviations: BMC, bone mineral content; NAFLD, nonalcoholic fatty liver disease; WMD, weighted mean difference.

fat content had a significant positive relationship with known or suspected NAFLD, whereas in girls, no such relationship was observed. However, until now, there has been no direct evidence to explain this difference. Genetic factors, biological differences, sample sizes, and other elements may contribute to this phenomenon. As a result, further studies need to explore this relationship between different genders.

However, there are several limitations of this meta-analysis. First, some confounders were not eliminated, and some included studies were missing essential data, such as the number of boys and girls, age, BMI, BMC, and BMD; thus, we did not conduct subgroup analyses. Second, we did not evaluate the severity of NAFLD, and the results we obtained included the range of this disease. Third, because few studies have been performed on this subject, after filtering the studies, only six studies were included in this meta-analysis. If more studies are conducted in the future, we will further study the subgroups. Finally, most studies were from western countries, only one was from Asia, so the results may not be generalizable to some regions; further research needs to be done.

Conclusion

This meta-analysis explored the concept of obese adolescents with NAFLD exhibiting a lower BMD. However, due to the quality and quantity of the included studies, further studies are needed to reveal the relationship between NAFLD and BMD in obese children.

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Disclosure

The authors report no conflicts of interest in this work.

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