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# Causal roles of circulating adiponectin in osteoporosis and cancers

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ABSTRACT

Circulating adiponectin has some association with the risk of osteoporosis and cancers, but their causal relationships remains elusive. Mendelian randomization (MR) study was used to explore the causal roles of circulating adiponectin in osteoporosis and cancers by using genome-wide association studies (GWASs) associated with circulating adiponectin, osteoporosis and cancers. Fifteen single nucleotide polymorphisms (SNPs) were used as instrumental variables for circulating adiponectin. Genetic predisposition to high circulating adiponectin was strongly associated with low femoral neck bone mineral density (FN-BMD, beta-estimate: -0.015, 95% CI: −0.023 to −0.006, SE: 0.004, P-value = 0.001), low forearm BMD (FA-BMD, beta-estimate: -0.027, 95% CI: −0.050 to −0.004, SE: 0.012, P-value = 0.023) and increased risk of breast cancer (beta-estimate: 0.011, 95% CI: 0.001 to 0.022, SE: 0.005, P-value = 0.031). There was limited evidence of the associations between circulating adiponectin and other outcomes (i.e. lumbar spine BMD [LS-BMD], colorectal cancer, liver cancer, lung cancer, bone cancer and prostate cancer). This study provides robust evidence that high circulating adiponectin is causally associated with low FN-BMD, low FA-BMD and increased risk of breast cancer, which may provide new insight to prevent and treat osteoporosis and breast cancer.

## 1. Introduction

Accumulating evidence suggests that excess adiposity is an important risk factor of many diseases such as osteoporosis and cancers [1–3]. Chronic inflammatory responses commonly occur in patients with obesity, and continued infiltration of macrophages and other immune cells into adipose tissues affects the secretion of adipokines [4]. As one kind of crucial adipokines, adiponectin has drawn an increasing attention due to the effect on type 2 diabetes and inflammatory responses [5–7].

Adiponectin displays valuable roles in the modulation of inflammatory responses which are associated with the regulation of osteoporosis and cancers [8–11]. Inflammation can lead to osteoporosis and aging-related bone loss, and inhibition of inflammation promotes bone formation and reduces the bone loss [10,12]. In addition, inflammation also results in the initiation and development of tumors by stimulating deoxyribonucleic acid (DNA) damage, chromosomal instability, tumor cell proliferation and resistance to apoptosis [11,13]. Previous studies documented the association between inflammation with some cancers such as colorectal cancer [14], liver cancer [15] and lung cancer [16]. Many signaling pathways including nuclear factor-kappa B (NF-kB) signaling pathway and reactive oxygen species (ROS) signaling pathway participated in the both regulation of osteoporosis and cancers [10,11,17].

Several studies reported that circulating adiponectin had some association with risk of osteoporosis and cancers, but these associations were inconclusive and may suffer from confounding factors and reverse causality [18–21]. For instance, some studies revealed that high circulating adiponectin was the risk factor of low bone mineral density (BMD) [19,22], but this finding was not supported by other observational studies [23,24]. In terms of breast cancer, the association between circulating adiponectin level and the risk for breast cancer was unraveled among 102 breast cancer patients and 100 healthy women [25]. Another study found the inverse association of circulating adiponectin with the risk of breast cancer among postmenopausal women, but this association was not significant among premenopausal women [26].

In order to avoid reverse causation and potential confounding factors, Mendelian randomization (MR) study has been developed to establish the causal relationship between exposure phenotype and outcome phenotype [27–32]. Statistical power of MR can be increased

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by using the two-sample MR study [29,33–35]. Circulating adiponectin, osteoporosis and cancers are highly polygenic traits according to the results of genome-wide association studies (GWASs) [36–42]. This two-sample MR study aims to explore the causal roles of circulating adiponectin in osteoporosis and cancers, which may provide new insights to prevent, diagnose and treat osteoporosis and cancers.

## 2. Methods

### 2.1. Genetic instrument for circulating adiponectin

The largest available GWAS meta-analysis associated with circulating adiponectin included 25 independent studies and 67,739 adult individuals of the following ancestries: (1) European, (2) East Asian, (3) African American and (4) Hispanic. Each single nucleotide polymorphism (SNP) was tested after adjusting for age, body mass index, sex and principal components that may result in possible population stratification. Circulating adiponectin levels were measured by enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) or dissociation-enhanced lanthanide fluoroimmunoassays (DELFIA) [36].

Initially, 18 SNPs ($P < 5 \times 10^{-8}$) were considered to have robust association with circulating adiponectin (Supplementary Table 1). Then, linkage disequilibrium (LD) between SNPs was measured using European samples from the 1000 Genomes project, and we removed three SNPs (rs3087866, rs145119400 and rs3865188) due to high LD ($r^2 \geq 0.001$). Finally, 15 SNPs were used as instrumental variables of circulating adiponectin (Supplementary Table 2).

### 2.2. Outcome data sources

Table 1 demonstrated the information of outcome data from several large GWASs. One large GWAS meta-analysis was conducted to explore the genetic variants associated with femoral neck BMD (FN-BMD), forearm BMD (FA-BMD) and lumbar spine BMD (LS-BMD) among 53,236 individuals of European ancestry [43]. We used the GWAS summary data reporting breast cancer (266,081 individuals) of European descent from the Breast Cancer Association Consortium [44], colorectal cancer (387,318 individuals), liver cancer (393,513 individuals), lung cancer (408,327 individuals) and bone cancer (408,665 individuals) of European descent from UK Biobank [39], as well as prostate cancer (140,254 individuals) of European descent from Prostate Cancer Association Group to Investigate Cancer Associated Alterations (PRACTICAL) consortium [45]. All participants were all from European descent except those associated with circulating adiponectin from predominantly European descent (mixed decent). Selected SNPs associated with circulating adiponectin and outcomes were presented in Supplementary Table 2.

### 2.3. Statistical analyses

Inverse variance weighted (IVW) meta-analysis of the Wald ratio was applied to study MR estimates of circulating adiponectin on each outcome. We also used the weighted median and MR-Egger regression methods to estimate their MR association. Cochrane's Q-statistic was used to assess the heterogeneity of SNP effects and $P < 0.05$ indicated significant heterogeneity. MR pleiotropy residual sum and outlier (MR-PRESSO) test was applied to evaluate the presence of pleiotropy and the effect was recalculated after removing SNPs outliers [46].

The ethical approval for each included GWAS was presented in the original publications. $P < 0.05$ indicated statistically significant difference. All analyses were performed in R V.4.0.4 by using the R packages of 'MendelianRandomization' [47], 'TwoSampleMR' [48] and 'MR-PRESSO' [49].

## 3. Results

### 3.1. Osteoporosis

We evaluated the causal effect of circulating adiponectin on FN-BMD, FA-BMD and LS-BMD in this MR analysis (Table 2). According to the IVW analysis, genetically high circulating adiponectin played a significant causal role in low FN-BMD (beta-estimate: -0.015, 95% CI: −0.023 to −0.006, SE: 0.004, P-value = 0.001, Fig. 1) and FA-BMD (beta-estimate: -0.027, 95% CI: −0.050 to −0.004, SE: 0.012, P-value = 0.023, Fig. 2), and the positive finding between circulating adiponectin and FN-BMD was further confirmed by weighted-median analysis (beta-estimate: -0.017, 95% CI: −0.029 to −0.005, SE: 0.006, P-value = 0.005, Fig. 1).

### 3.2. Cancers

This MR study explored the causal roles of circulating adiponectin in the risk of breast cancer, colorectal cancer, liver cancer, lung cancer, bone cancer and prostate cancer (Table 2). According to weighted-median analysis, high circulating adiponectin showed substantially causal effect on the increased risk of breast cancer (beta-estimate: 0.011, 95% CI: 0.001 to 0.022, SE: 0.005, P-value = 0.031), but it was not confirmed in the IVW analysis (beta-estimate: 0.005, 95% CI: −0.007 to 0.016, SE: 0.006, P-value = 0.430, Fig. 3). In addition, these IVW analyses found that circulating adiponectin demonstrated no remarkable MR association with colorectal cancer (beta-estimate: 0.014, 95% CI: −0.012 to 0.041, SE: 0.013, P-value = 0.293), liver cancer (beta-estimate: 0.009, 95% CI: −0.055 to 0.236, SE: 0.074, P-value = 0.223), lung cancer (beta-estimate: 0.016, 95% CI: −0.026 to 0.059, SE: 0.022, P-value = 0.456), bone cancer (beta-estimate: -0.013, 95% CI: −0.236 to

**Table 1**
Details of studies and datasets used for analyses.

| | | Traits | Samples size | Population | Consortium or cohort study (link URL) |
|---|---|---|---|---|---|
| Exposure | Adiponectin | Adiponectin | 67,739 | Predominant European (mixed) | Meta-analysis of 25 studies |
| Outcomes | Osteoporosis | Femoral neck BMD | 53,236 | European | GEnetic Factors for OSteoporosis (GEFOS) Consortium (http://www.gefos.org) |
| | | Forearm BMD | 53,236 | European | |
| | | Lumbar spine BMD | 53,236 | European | |
| | Cancers | Breast cancer | 266,081 | European | Breast Cancer Association Consortium (http://bcac.ccge.medschl.cam.ac.uk/) |
| | | Colorectal cancer | 387,318 | European | UK Biobank (https://www.leelabsg.org/resources) |
| | | Liver cancer | 393,513 | European | |
| | | Lung cancer | 408,327 | European | |
| | | Bone cancer | 408,665 | European | |
| | | Prostate cancer | 140,254 | European | Prostate Cancer Association Group to Investigate Cancer Associated Alterations (PRACTICAL) Consortium (http://practical.icr.ac.uk/blog/) |

**Table 2**
Mendelian randomization estimates of adiponectin on outcomes.

| Variables | IVW | | | | | | Weighted median | | | | MR-Egger | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Estimate | SE | 95% CI | P-value | Q value | $I^2$ | Heterogeneity P value | Estimate | SE | 95% CI | P-value | Estimate | SE | 95% CI | P-value | Intercept | SE | 95% CI | Pleiotropy P value |
| Osteoporosis | | | | | | | | | | | | | | | | | | | |
| FN-BMD | -0.015 | 0.004 | −0.023, −0.006 | 0.001 | 10.445 | 0.00% | 0.729 | −0.017 | 0.006 | −0.029, −0.005 | 0.005 | −0.006 | 0.008 | −0.022, 0.009 | 0.422 | −0.005 | 0.004 | −0.012, 0.003 | 0.228 |
| FA-BMD | −0.027 | 0.012 | −0.050, −0.004 | 0.023 | 19.374 | 27.70% | 0.151 | −0.027 | 0.014 | −0.055, 0.000 | 0.050 | −0.024 | 0.021 | −0.066, 0.017 | 0.251 | −0.002 | 0.010 | −0.021, 0.018 | 0.875 |
| LS-BMD | −0.004 | 0.006 | −0.016, 0.008 | 0.507 | 19.008 | 26.30% | 0.165 | −0.012 | 0.008 | −0.027, 0.003 | 0.131 | 0.004 | 0.011 | −0.017, 0.026 | 0.710 | −0.005 | 0.005 | −0.015, 0.006 | 0.374 |
| Cancers | | | | | | | | | | | | | | | | | | | |
| Breast cancer | 0.005 | 0.006 | −0.007, 0.016 | 0.430 | 35.615 | 60.70% | 0.001 | 0.011 | 0.005 | 0.001, 0.022 | 0.031 | 0.000 | 0.011 | −0.021, 0.020 | 0.966 | 0.003 | 0.005 | −0.007, 0.013 | 0.572 |
| Colorectal cancer | 0.014 | 0.013 | −0.012, 0.041 | 0.293 | 15.754 | 11.10% | 0.329 | 0.010 | 0.017 | −0.023, 0.043 | 0.568 | 0.056 | 0.023 | 0.012, 0.101 | 0.013 | −0.024 | 0.011 | −0.045, −0.003 | 0.025 |
| Liver cancer | 0.009 | 0.074 | −0.055, 0.236 | 0.223 | 15.298 | 8.50% | 0.358 | 0.138 | 0.094 | −0.046, 0.323 | 0.143 | 0.183 | 0.135 | −0.081, 0.447 | 0.174 | −0.053 | 0.064 | −0.178, 0.073 | 0.408 |
| Lung cancer | 0.016 | 0.022 | −0.026, 0.059 | 0.456 | 19.153 | 26.90% | 0.159 | 0.011 | 0.025 | −0.038, 0.061 | 0.650 | 0.021 | 0.040 | −0.058, 0.100 | 0.607 | −0.003 | 0.019 | −0.040, 0.035 | 0.892 |
| Bone cancer | −0.013 | 0.114 | −0.236, 0.209 | 0.906 | 32.411 | 56.80% | 0.004 | 0.009 | 0.105 | −0.197, 0.215 | 0.931 | −0.042 | 0.211 | −0.456, 0.371 | 0.841 | 0.017 | 0.100 | −0.018, 0.213 | 0.869 |
| Prostate cancer | 0.002 | 0.005 | −0.008, 0.011 | 0.742 | 14.884 | 5.90% | 0.386 | 0.008 | 0.007 | −0.005, 0.022 | 0.224 | 0.001 | 0.009 | −0.017, 0.020 | 0.878 | 0.000 | 0.004 | −0.009, 0.009 | 0.978 |

0.209, SE: 0.114, P-value = 0.906) or prostate cancer (beta-estimate: 0.002, 95% CI: −0.008 to 0.011, SE: 0.005, P-value = 0.742, Fig. 4), which were also confirmed by weighted-median analyses (Table 2).

### 3.3. Assumptions evaluation and sensitivity analyses

We found little evidence of directional pleiotropy except the potential pleiotropic effect between circulating adiponectin and colorectal cancer (MR-Egger intercept P-value = 0.025, Table 2). Significant heterogeneity remained for breast cancer and bone cancer. MR-PRESSO method was performed to identify 2 outliers (rs13303 and rs4805885) for breast cancer and 2 outliers (rs11057405 and rs4805885) for bone cancer among the 15 SNP instrumental variables associated with circulating adiponectin (Table 3). No outliers were found for the association between circulating adiponectin and colorectal cancer, which confirmed no pleiotropy between them.

After excluding these outlying SNP variants, the remarkable MR associations were confirmed between circulating adiponectin and BMD outcomes (i.e. FN-BMD and FA-BMD, Figs. 1 and 2). In addition, high circulating adiponectin was confirmed to have a causal effect on increased risk of breast cancer (beta-estimate: 0.014, 95% CI: 0.005 to 0.023, SE: 0.005, P-value = 0.002, Fig. 3 and Table 3). The MR associations between circulating adiponectin with other outcomes were not changed after excluding the outlying SNP variants (Table 3).

## 4. Discussion

Our MR study unraveled the robustly causal roles of high circulating adiponectin in low FN-BMD, low FA-BMD and increased risk of breast cancer, and these strong MR associations were confirmed by the multiple sensitivity analyses. These positive findings indicated that the reduction in circulating adiponectin may provide new insight to prevent and treat osteoporosis and breast cancer. We found no causal effect of circulating adiponectin on LS-BMD, colorectal cancer, liver cancer, lung cancer, bone cancer or prostate cancer.

As one systemic skeletal disease, osteoporosis has the features of low bone mass, BMD and bone strength which may result in the increased risk of fracture [50,51]. Previous studies examined the association between circulating adiponectin and osteoporosis, but the results were conflicting [18,19,22,23]. One observational study involving 386 women revealed the negative association between circulating adiponectin and FN-BMD (P = 0.043) [19]. Another case-control study found the relationship between circulating adiponectin and LS-BMD in postmenopausal women [18]. One large population-based cohort involving 1735 women revealed that high circulating adiponectin resulted in the decreased BMD after adjusting for body fat [22]. However, another study displayed no association between serum adiponectin and BMD among 320 men [23], and this finding was supported by one study involving 200 premenopausal women [24].

In order to prevent the confounding factors and reverse causality of observational studies, MR studies have become an increasingly important approach to ascertain the causes of diseases [52]. Our large-scale MR study was performed among 67,739 individuals associated with circulating adiponectin and 53,236 individuals associated with BMD. Totally, 15 SNPs ($P < 5 \times 10^{-8}$) were used as instrumental variables for circulating adiponectin. The results provided the robust evidence for the causal roles of high circulating adiponectin in low FN-BMD and FA-BMD, which was confirmed by multiple sensitivity analyses.

Adiponectin has emerged as an important element in the regulation of osteoporosis. The key cytokine receptor activator of nuclear factor-kappa B ligand (RANKL) is widely accepted to induce osteoclast differentiation and osteoclastogenesis, which subsequently leads to bone resorption [53,54]. RANKL inhibitor is beneficial to restore bone mass in osteoporotic mice and patients [54,55]. Adiponectin is found to significantly increase the expression of RANKL in the dose and time-dependent manner [56,57], which subsequently aggravates

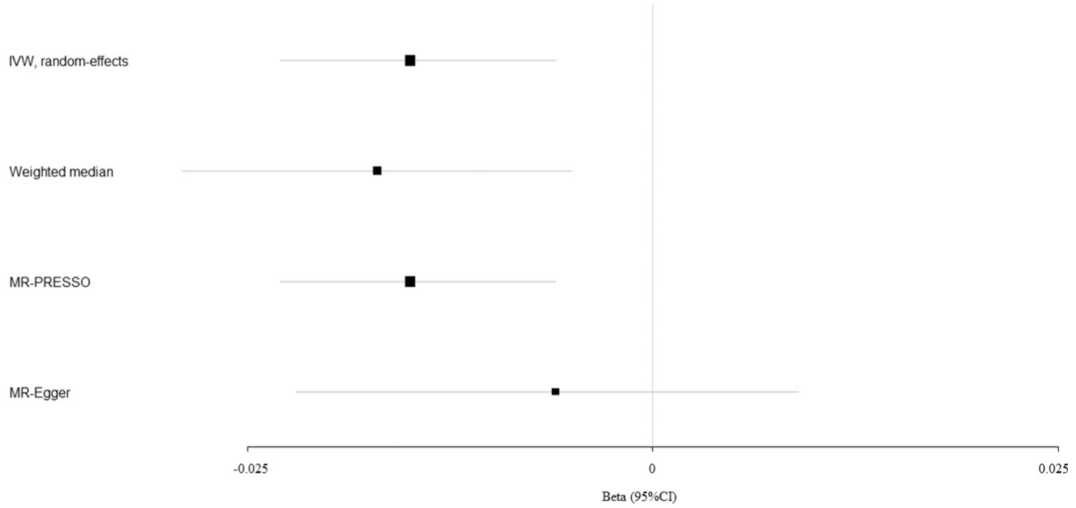


**Fig. 1.** Beta (95% CIs) for causal association between circulating adiponectin and FN-BMD through multiple analyses.

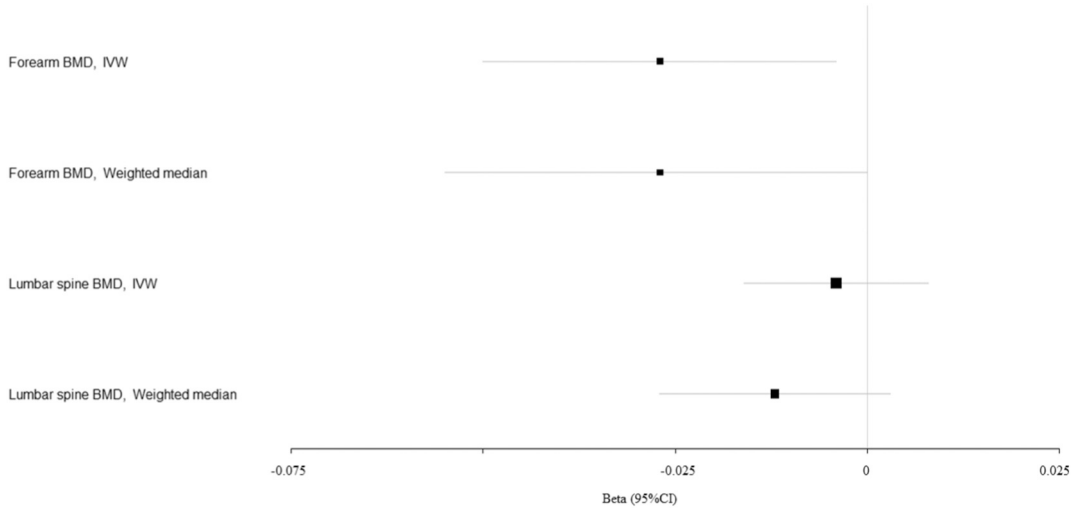


**Fig. 2.** Beta (95% CIs) for causal influence of circulating adiponectin on FA-BMD and LS-BMD through multiple analyses.

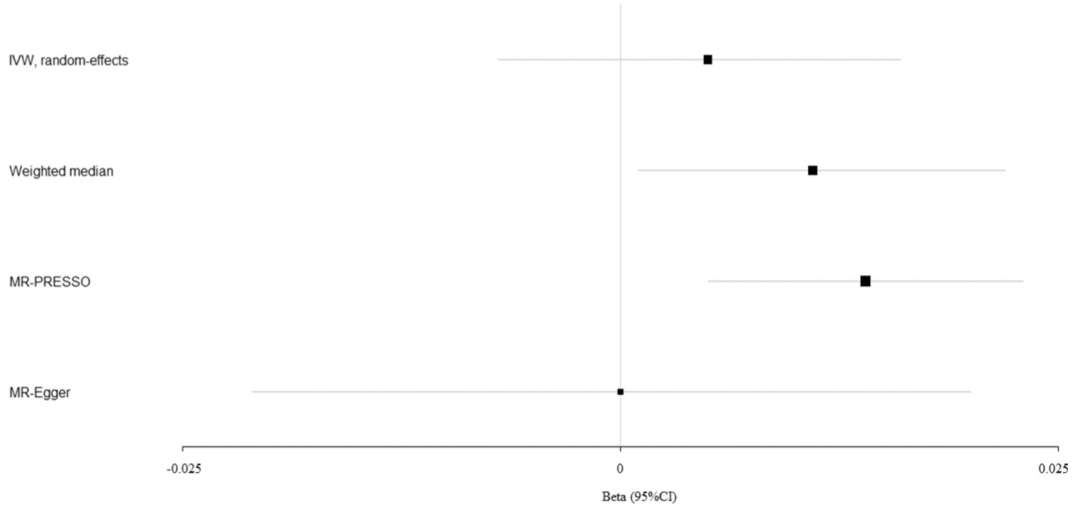


**Fig. 3.** Beta (95% CIs) for causal association between circulating adiponectin and breast cancer through multiple analyses.

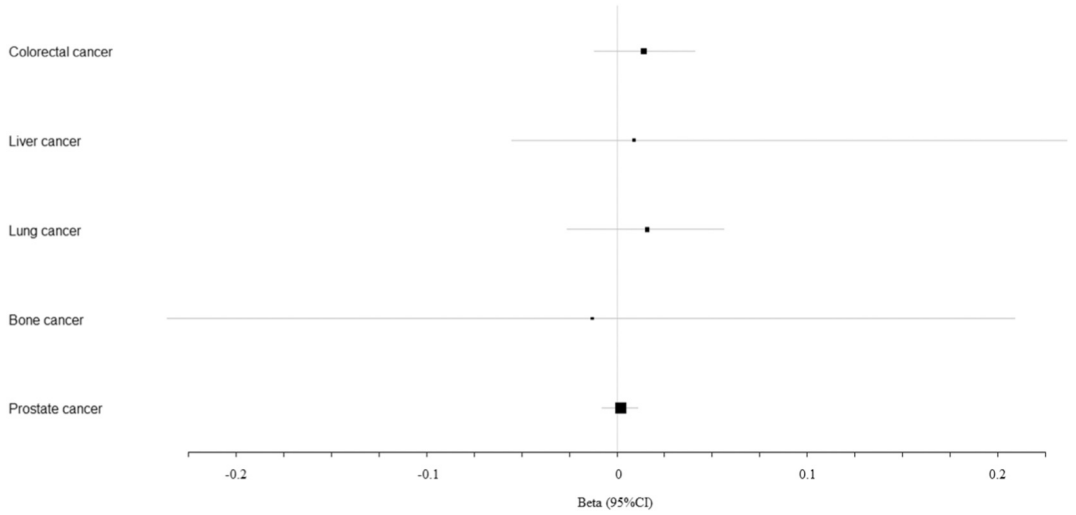


**Fig. 4.** Beta (95% CIs) for causal influence of circulating adiponectin on colorectal cancer, liver cancer, lung cancer, bone cancer and prostate cancer.

**Table 3**
Mendelian randomization estimates between adiponectin and outcomes after excluding outliers detected by MR-PRESSO.

| Outcomes | Estimate | SE | 95% CI | P-value |
|---|---|---|---|---|
| Breast cancer excluding 2 outliers (rs13303, rs4805885) | 0.014 | 0.005 | 0.005, 0.023 | 0.002 |
| Bone cancer excluding 2 outliers (rs11057405, rs4805885) | 0.075 | 0.089 | −0.100, 0.249 | 0.403 |

osteoporosis and explains the inverse finding between high serum adiponectin and low BMD in this MR study.

Some studies reported the inconsistent association between circulating adiponectin and cancer risk including endometrial, colorectal, renal cell carcinoma and pancreatic cancer, which may be also caused by confounding factors and reverse causality [58–61]. For instance, Miyoshi et al. found that circulating adiponectin levels had strong association with the risk of breast cancer [25]. Mantzoros et al. documented that adiponectin levels had no influence on the incidence of breast cancer in premenopausal women [26].

Our two-sample MR study included large-scale population samples associated with breast cancer, colorectal cancer, liver cancer, lung cancer, bone cancer and prostate cancer. The results confirmed the positive causal association between high circulating adiponectin and increased risk of breast cancer, but circulating adiponectin unraveled no causal impact on colorectal cancer, liver cancer, lung cancer, bone cancer or prostate cancer. Considering the possible mechanisms of circulating adiponectin to increase the risk of breast cancer, overexpression of receptor activator of nuclear factor-kappa B (RANK)/RANKL leads to the interferences in acinar formation of breast tissue and impairs the development of growth arrest in DNA-damaged cells [62]. High circulating RANKL levels are associated with increased risk of breast cancer [63] and adiponectin can significantly improve RANKL levels [64]. These may account for the MR association between high serum adiponectin and increased risk of breast cancer in our study.

There are several important strengths. This study aims to explore the causal roles of circulating adiponectin in osteoporosis and the risk of cancers, and prevents some limitations of reverse causation and potential confounding factors. All observed causal associations are not affected by directional pleiotropy. Multiple sensitivity analyses are conducted to study the influence of pleiotropy on causal estimates. We should also consider several limitations. Firstly, all included participants are of predominantly European origin, but it is unknown that whether our findings are suitable to other populations. Secondly, the positive casual roles of circulating adiponectin on FN-BMD and FA-BMD are not consistent with the relationship between circulating adiponectin and LS-BMD, but the related mechanisms are not clear. Thirdly, serum adiponectin is tested by different methods including ELISA, RIA and DELFIA, which may produce some bias.

## 5. Conclusion

This two-sample MR study confirms that high circulating adiponectin is a significantly causal factor for osteoporosis and breast cancer, which may help prevent, diagnose and treat these two diseases.

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## CRediT authorship contribution statement

BH, JQZ, MZZ, LFY and WH conducted study design, data collection, and statistical analysis. BH, JQZ, MZZ, ZXQ, YSO and WH conducted data interpretation, manuscript preparation, and literature search. BH conducted funds collection.

## Declaration of competing interest

The authors declared that there was no conflict of interest.

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*Data availability*

Data supporting the findings of this study were available within the paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2021.116266.

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