

## Review Article

# Glucose metabolic disorder in primary hyperparathyroidism: a systematic review and meta-analysis

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**Abstract:** *Background:* Primary hyperparathyroidism (PHPT) is associated with increased morbidity and mortality of cardiovascular disease (CVD). Studies have demonstrated that patients with PHPT have more metabolic disorders than age-matched healthy controls, which mainly include obesity, insulin resistance, dyslipidemia, hyperglycemia and hypertension. In this meta-analysis, metabolic disorders of PHPT patients were systematically reviewed. *Methods:* Databases were searched for studies published between 2005 and 2017 that reported body mass index (BMI), insulin resistance and blood glucose in PHPT patients and healthy controls. *Results:* A total of nine eligible studies were identified. Compared to healthy controls, PHPT patients had higher levels of plasma insulin (SMD = 0.37, CI: 0.23~0.52,  $P = 0.014$ ) and insulin resistance index (HOMA-IR) (SMD = 0.65, CI: 0.27~1.02,  $P = 0.009$ ). However, BMI was not statistically different between PHPT patients and healthy controls (SMD = 0.09, CI: -0.14~0.31,  $P = 0.32$ ). Although fasting blood glucose (FBG) levels of PHPT patients were similar to healthy controls (SMD = 0.06, CI: -0.36~0.47,  $P = 0.21$ ), subgroup analysis showed that hypercalcemic primary hyperparathyroidism (HPHPT) patients had higher FBG levels than healthy controls (SMD = 0.43, CI: 0.18~0.68,  $P = 0.025$ ). *Conclusions:* Compared with healthy controls, PHPT patients had heavier insulin resistance, but only hypercalcemia PHPT patients had higher FBG levels. There was no significant difference in BMI between PHPT patients and healthy controls.

**Keywords:** Primary hyperparathyroidism, meta-analysis, insulin resistance, fasting blood glucose, body mass index

## Introduction

Cardiovascular disease (CVD) leads to nearly one third of all deaths globally [1]. Plenty of risk factors are involved in the development of CVD. These risk factors mainly include hyperglycemia, obesity, hypertension and dyslipidemia. Additionally, insulin resistance plays an important role in CVD associated with metabolic syndrome (MetS) in obese patients [2]. As an endocrine disease with the core disorder of calcium-phosphorus metabolism, primary hyperparathyroidism (PHPT) is mainly manifested in the mobilization of bone calcium and abnormal calcium deposition in the whole body. PHPT is associated with increased morbidity and mortality of CVD [3]. Recent evidence indicates that PHPT is associated with metabolic disorders such as glucose intolerance, obesity, insulin

resistance and decreased insulin secretion, and these metabolic disorders are presumed to be the cause of increased mortality of CVD in PHPT patients [4-6]. A meta-analysis concludes that PHPT patients have a greater body weight than their eucalcemic peers, and increased body weight may contribute to the relationship between PHPT and some cardiovascular complications. However, other studies demonstrate a converse association [7, 8]. Therefore, studies on the association between PHPT and metabolic disorders have yielded conflicting results. A further analysis on this association can be helpful in reducing the mortality of CVD in PHPT patients.

Up to now, no previous meta-analysis has evaluated the difference of glucose, body mass index (BMI) and insulin resistance between

PHPT patients and healthy controls. In this meta-analysis, the association between PHPT and these metabolic disorders was systematically evaluated.

## Materials and methods

### *Searching strategy*

Our data sources included PubMed, Medline, Embase, The Cochrane Library and Web of Science for all articles between 2005 and 2017. The following keywords were used in the online searching, including “primary hyperparathyroidism”, “glucose”, “diabetes”, “diabetes mellitus”, “weight”, “obesity”, “insulin resistance”, “insulin” and “metabolic syndrome”. The searching was limited to English. Additionally, hand searching was performed to identify potentially relevant studies.

### *Inclusion criteria and exclusion criteria*

The studies which met the following criteria were included in this meta-analysis: (1) case-control or cohort studies; (2) studies aimed at evaluating the association between PHPT and risk factors correlated with MS; (3) glucose metabolism parameters as study variables; and (4) studies providing presentation of quantitative data (i.e., the number of cases and controls, mean and standard deviation).

The exclusion criteria included: (1) studies in which participants underwent parathyroidectomy; (2) studies in which controls were selected from a population with comorbidities likely to impact MS; (3) studies that were not clear whether cases were primary hyperparathyroidism or secondary hyperparathyroidism; (4) case-only studies, review articles, commentaries, editorials, or case reports; (5) case groups and control groups were not comparable in age and gender.

### *Data extraction*

Three reviewers (Qin Sun, Min Zhang and Tao Zhang) were responsible for extracting data from the selected articles independently. They compared the results and reached consistencies on all items. Characters extracted from the studies included year of publication, author, study type, cohort/study name, total number of cases and controls, participants' gender, aver-

age age at baseline, means of metabolic factors [BMI, blood glucose, plasma insulin and insulin resistance index (HOMA-IR)] and their standard error (SE).

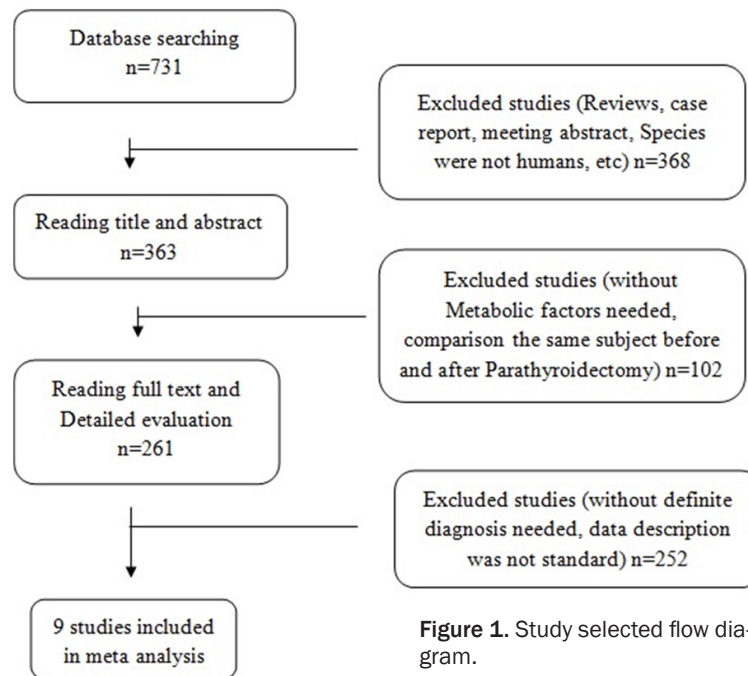
The quality of individual records was assessed with Newcastle-Ottawa quality-assessment scale [9]. Each study was assigned with 0~9 “stars” (more stars meant higher quality) by the reviewers to ensure the accuracy of extraction.

This meta-analysis was conducted using STATA statistical software version 12.0 (STATA Corp LP, College Station, TX, USA). Mean differences (MD) of BMI, fasting blood glucose (FBG), fasting insulin and HOMA-IR were calculated for all eligible studies. Heterogeneity was evaluated through the  $\chi^2$ -based Cochran's Q statistic and  $I^2$  statistic. The percentages of  $I^2$  around 25%, 50% and 75% indicated low, medium and high heterogeneity, respectively. The fixed-effects model was used to calculate the pooled MD when there was no significant heterogeneity ( $P$  more than 0.10 and  $I^2$  less than 50%) among the included studies; otherwise, the random-effects model was employed [10]. The potential publication bias was tested using both Begg's rank correlation test and Egger's linear regression test [11, 12].

## Results

### *Selection of studies*

Initially, 731 citations were identified from the data sources. After screening with inclusion and exclusion criteria, a total of nine studies were include in this meta-analysis (**Figure 1**). All of them were case-control studies, in which patients were definitely diagnosed with PHPT and controls were excluded from PHPT by parathyroid hormone (PTH). PHPT patients were divided into hypercalcemic primary hyperparathyroidism (HPHPT) and normocalcemic primary hyperparathyroidism (NPHPT) based on serum calcium levels [13]. Among them, four studies compared metabolic factors between HPHPT patients and controls [5, 7, 14, 15], two studies compared metabolic factors between NPHPT patients and controls [8, 16], 1 study provided available data for HPHPT patients, NPHPT patients and controls [4], and the last two studies did not clearly indicate whether patients were HPHPT or NPHPT [17, 18]. All nine studies in total reported data on 521 PHPT



**Figure 1.** Study selected flow diagram.

patients and 455 controls. The detailed characteristics of the included studies are demonstrated in **Table 1**. Overall, the quality of the included studies was intermediate to high (**Table 2**).

## Metabolic results in comparable groups

All nine studies reported usable data on FBG levels, and the FBG levels of the PHPT patients were similar to healthy controls (SMD = 0.06, 95% CI: -0.36~0.47,  $P = 0.21$ ;  $I^2 = 88.3\%$ ,  $P < 0.005$ ). Subgroup analysis was then performed. Three studies involving 56 NPHPT patients and 64 healthy controls showed no significant difference in FBG levels between NPHPT patients and healthy controls (SMD = -1.38, 95% CI: -3.89~0.45,  $P = 0.17$ ;  $I^2 = 96.6\%$ ,  $P < 0.005$ ). Five studies involving 265 HPHPT patients and 200 controls showed that HPHPT patients had higher FBG levels than healthy controls (SMD = 0.43, 95% CI: 0.18~0.68,  $P = 0.025$ ;  $I^2 = 36.1\%$ ,  $P = 0.181$ ). The results are demonstrated in **Figure 2**.

All nine studies reported usable data on BMI. Initial analysis indicated that there was no significant difference in BMI between PHPT patients and healthy controls (SMD = 0.09, 95% CI: -0.14~0.31,  $P = 0.32$ ;  $I^2 = 61.1\%$ ,  $P = 0.006$ ). Subgroup analysis further showed no significant difference between BMI of NPHPT or

HPHPT patients and healthy controls. The results are demonstrated in **Figure 3**.

Six studies reported usable data on plasma insulin, and five studies reported usable data on HOMA-IR. Both plasma insulin and HOMA-IR were higher in PHPT patients than in healthy controls (plasma insulin: SMD = 0.37, 95% CI: 0.23~0.52,  $P = 0.014$ ;  $I^2 = 0\%$ ,  $P = 0.688$ ; HOMA-IR: SMD = 0.65, 95% CI: 0.27~1.02,  $P = 0.009$ ;  $I^2 = 67.5\%$ ,  $P = 0.009$ ). The results are demonstrated in **Figure 4A** and **4B**.

## Publication bias

We assessed the publication bias of the primary outcomes. For the included studies, the

degree of asymmetry was not statistically significant as Begg's test demonstrated ( $P = 0.92$ ), which indicated a small publication bias. The results are shown in **Figure 5**.

## Sensitivity analysis

Sensitivity analysis demonstrated that no individual significantly affected the difference of FBG levels, BMI, plasma insulin and HOMA-IR.

## Discussion

As an endocrine disease with the core disorder in calcium-phosphorus metabolism, PHPT is mainly manifested in the mobilization of bone calcium and abnormal calcium deposition in the whole body [3]. Most of PHPT patients have hypercalcemia, also known as hypercalcemic primary hyperparathyroidism (HPHPT), and the others are defined as normocalcemic primary hyperparathyroidism (NPHPT) because of normal blood calcium levels. Some NPHPT patients eventually develop hypercalcemia, however, other patients can maintain normal levels of blood calcium and parathyroid hormone (PTH) even when target organ damages occur, such as renal stones and osteoporosis [9, 13].

Recent evidence indicate that PHPT is also correlated with metabolic disorders and some components of MS, such as glucose intoler-

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**Table 1.** Study characteristics

Study	Male (n, %)		Age (year)		PTH (pg/ml)		Serum 25OHD (ng/ml)		Serum Calcium (mg/dl)	
	PHPT	Control	PHPT	Control	PHPT	Control	PHPT	Control	PHPT	Control
2006 Ayturk S	14, 22.9%	12, 15%	62.0 ± 10.0	59.8 ± 10.0	156 ± 67	52 ± 14	32.2 ± 19.9	29.9 ± 12.7	10.2 ± 0.7	9.5 ± 0.5
2007 Delfini E	11, 16.4%	10, 21.7%	57.9 ± 12.2	58.1 ± 12.9	109 ± 79.6	29 ± 2.3	-	-	11.1 ± 1.1	9.4 ± 0.34
2009 Tassone F	29, 23.8%	14, 23.0%	59.3 ± 13.6	48.6 ± 14.0	203.2 ± 145.4	-	-	-	11.2 ± 1.0	9.2 ± 0.4
2009 Luboshitzky R	29, 20.9%	24, 21.6%	56.2 ± 11.8	55.6 ± 9.9	164.7 ± 118.0	45.2 ± 15.6	-	-	10.8 ± 0.7	9.6 ± 0.4
2011 Ishay A	11, 32.4%	8, 19.1%	51.0 ± 11.8	49.9 ± 3.2	222.9 ± 189.8	48.8 ± 13.4	-	-	11.2 ± 0.7	9.5 ± 0.4
2012 Cakir I	-	-	49.9 ± 2.4	48.3 ± 1.8	148.6 ± 19.0	49.5 ± 2.2	54.5 ± 12.4	-	9.7 ± 0.1	9.2 ± 0.1
2016 Mendonça ML	-	-	51.1 ± 11.3	50.1 ± 9.4	459.8 ± 462.2	44.5 ± 16.7	18.3 ± 4.8	24.7 ± 3.9	11.9 ± 1.1	9.6 ± 0.7
2017 Mesquita PN	-	-	65.15 ± 7.71	61.06 ± 7.65	100.58 ± 29.83	30.26 ± 12.0	35.32 ± 8.42	26.11 ± 8.9	9.28 ± 1.05	8.28 ± 0.45
2016 Yener Ozturk F										
HPHPT	2, 8%	9, 30%	52.88 ± 11.71	53.63 ± 7.43	91.61 ± 17.31	47.84 ± 9.49	17.04 ± 11.32	-	9.71 ± 0.34	9.58 ± 0.32
NPHPT	4, 16.7%	9, 30%	56.63 ± 12.70	53.63 ± 7.43	170.28 ± 111.26	47.84 ± 9.49	13.51 ± 9.01	-	11.52 ± 1.30	9.58 ± 0.32

PTH: parathyroid hormone, 25OHD: 25-hydroxyvitamin D, PHPT: Primary hyperparathyroidism patients, HPHPT: hypercalcemic primary hyperparathyroidism group, NPHPT: normocalcemic primary hyperparathyroidism group.

**Table 2.** Study quality

Study	Representativeness of the cases	Case independent validation	Selection of controls	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cases and controls	Same method of ascertainment for cases and controls	Same non-Response rate	conclusion
2006 Ayturk S	*	*		*	*	*	*		6*
2007 Delfini E	*	*			*	*	*	*	6*
2009 Luboshitzky R	*	*	*		*	*	*	*	7*
2009 Tassone F	*	*			*	*	*	*	6*
2011 Ishay A	*	*	*		*	*	*	*	7*
2012 Cakir I	*	*		*	*	*	*	*	7*
2016 Mendonça ML	*	*			*	*	*	*	6*
2016 Yener Ozturk F	*	*			*	*	*	*	6*
2017 Mesquita PN	*	*			*	*	*	*	6*

Newcastle-Ottawa quality-assessment scale was employed to assess the quality of included studies. The scale has 8 multiple choice questions, each question have 2 to 3 choices. "High" quality choice is identified with a "\*", which indicates "high quality literature". The more "\*" an literature is marked with, the better its quality.

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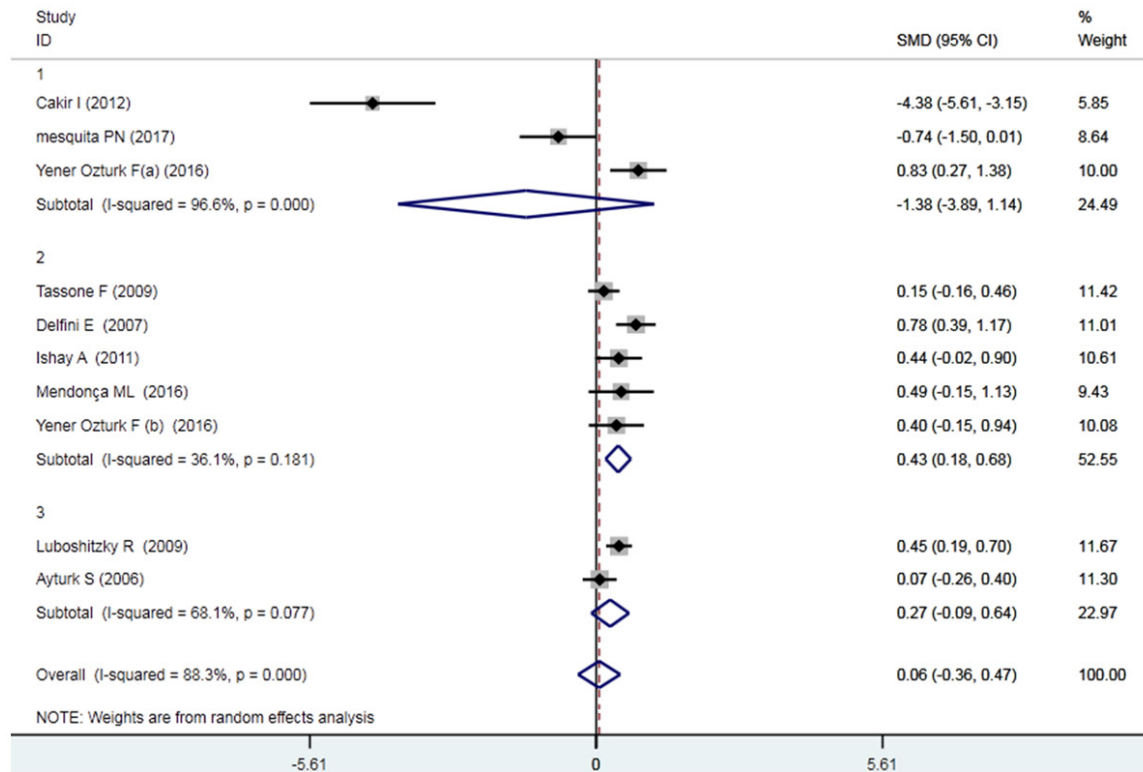


Figure 2. SMD in FBG in studies of PHPT and eucalcemic controls.

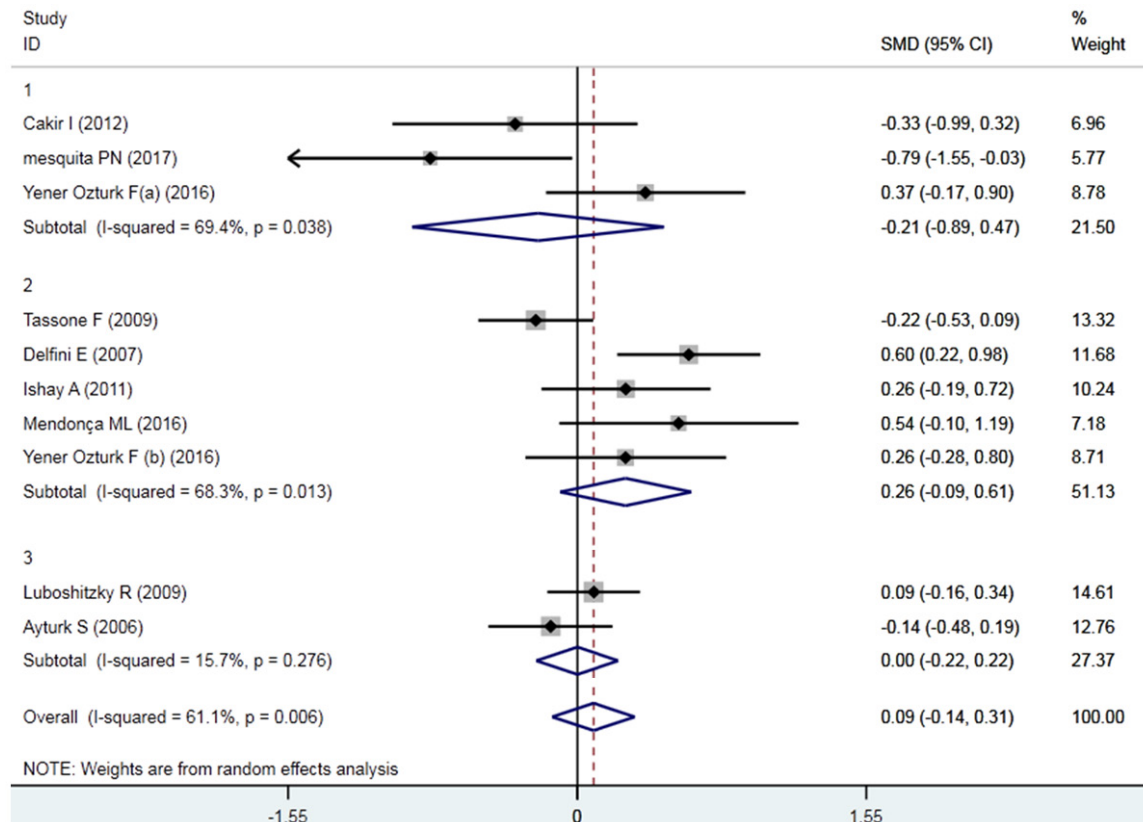
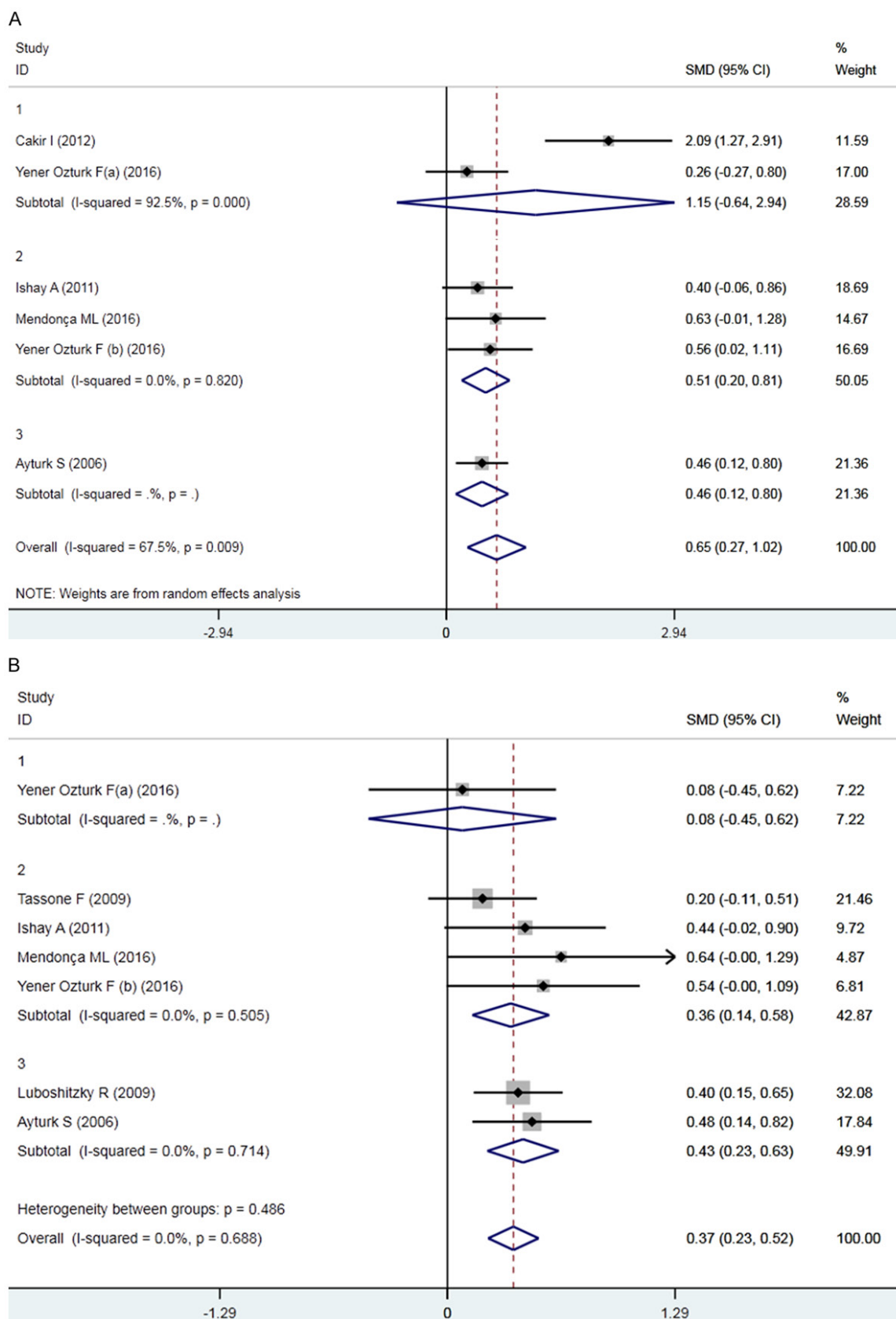


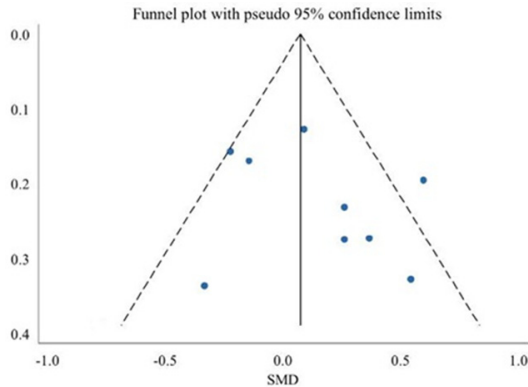
Figure 3. SMD in BMI in studies of PHPT and eucalcemic controls.



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**Figure 4.** A. SMD in HOMA index in studies of PHPT and eucalcemic controls; B. SMD in insulin in studies of PHPT and eucalcemic controls.



**Figure 5.** Begg's funnel plot of publication bias for this meta-analysis.

ance, obesity, insulin resistance and reduced insulin secretion [19]. In addition, PHPT is correlated with an increased risk of diabetes, cardiovascular mortality and stroke [6]. A meta-analysis has indicated that weight gain can elevate cardiovascular mortality [20]. However, until now no meta-analysis studies have been performed to assess the association between PHPT and other components of MS, such as glucose intolerance and insulin resistance. In this paper, we used meta-analysis to determine the difference in insulin resistance, insulin levels, BMI and glucose between patients with PHPT and healthy controls. To our knowledge, this was the first meta-analysis analyzing these metabolic disorders in patients with PHPT.

Our results demonstrated no significant difference in BMI between PHPT patients and healthy controls, which was inconsistent with the results of Bolland's study [20]. This is likely explained by the fact that BMI was used as the criteria for obesity instead of body weight which was used in Bolland's study. Furthermore, controls with matched body weight were used in all of the nine studies that were included in our meta-analysis in order to reduce confounding effects of body weight on insulin resistance and other metabolic disorders. Although no significant difference was found in BMI between PHPT and controls, PHPT patients had an average BMI greater than 25 in all nine studies included in our meta-analysis, and BMI greater than 28 was seen in six studies. Therefore, we could not conclude that there was no significant difference in obesity between patients with PHPT and healthy controls. In consideration of an average BMI greater than 25 in all

the included studies, it was likely that PHPT patients tended to be overweight or even obese [21].

Our results also showed that insulin resistance was more severe in PHPT patients than in healthy controls according to fasting plasma insulin and HOM-IR. This difference in insulin resistance was independent of body weight because body weight was matched between groups. Subsequent subgroup analysis indicated that insulin resistance was more severe in both HPHPT and NPHPT than in healthy controls.

Overweight or obese PHPT patients tend to have insulin resistance, and these patients may have abnormal glucose levels. Although not widely accepted, FBG levels of PHPT patients were shown to be elevated in some studies. In our study, no significant difference was found in FBG between PHPT patients and controls. However, subgroup analysis showed that FBG was significantly elevated in HPHPT patients compared with healthy controls, while no significant difference was shown between NPHPT patients and healthy controls. This supports the speculation that hypercalcemia may be responsible for hyperglycemia in hyperparathyroidism [22, 23].

A critical question that arises from this study is the mechanism of the association between PHPT and body weight. The causal relationship can make sense in either direction. There is evidence that hypercalcemia or increased intracellular calcium concentrations in adipocytes cause insulin resistance and inhibits lipolysis in NPHPT patients [24], and PTH elevates intracellular calcium in many cell types [25, 26]. It is also possible that PTH influences adipocyte differentiation, because PTH acts directly on osteoblasts [26, 27]. These observations imply that increased PTH leads to increased fat mass, which induces increased insulin resistance. Therefore, insulin resistance may be a consequence of PHPT, and is likely to be corrected by parathyroidectomy [28-30].

An alternative explanation for our findings is that increased body weight is involved in the development of PHPT. In many cases, 25-hydroxyvitamin D levels are inversely correlated with body weight, probably because vitamin D is sequestered by adipose tissue and is fat soluble [31]. Thus, increased body weight

may result in deficiency of vitamin D, which increases the risk of developing parathyroid adenomata [32, 33]. Leptin is mainly secreted by the white adipose tissue, and its circulating levels are positively correlated with fat mass. Studies demonstrate that the leptin receptor exists in the cytoplasm of the parathyroid chief cells, and high leptin levels in obese people may increase PTH secretion from the parathyroid chief cells [34, 35].

Hyperglycemia occurs gradually along with functional defects of Islet  $\beta$ -cells induced by insulin resistance [36]. NPHPT is thought to be the early stage of PHPT and will progress into HPHPT in some cases [37]. Normal blood glucose level in NPHPT is likely explained by the fact that impairment of Islet  $\beta$ -cell function due to insulin resistance is relatively mild during the early stage of PHPT. Hyperglycemia may develop when Islet  $\beta$ -cell function is substantially impaired because of long term insulin resistance in HPHPT.

Parathyroidectomy is an effective treatment for PHPT patients, and normalization of PTH and blood calcium levels is considered an indicator of successful surgery. According to current guidelines, parathyroidectomy is recommended for HPHPT patients, whilst close follow-up is an option for NPHPT patients without complications such as ectopic calcium precipitation, renal stones and loss of bone mass, or NPHPT patients who are reluctant to undergo surgery [3, 13]. The findings of our study demonstrated that NPHPT patients had increased risk of obesity and insulin resistance, which could elevate cardiovascular mortality. Therefore, it might be recommended that NPHPT patients have timely parathyroidectomy at the early stage, i.e. prior to development of obesity and insulin resistance.

Beyond doubt, our study had some limitations. A meta-analysis could not solve inherent confounding problems in the included studies, which might underestimate or exaggerate the effects. There was a lack of available robust trials and it is a challenge to extract reported data from the included studies. Not all identified studies were included because of different units and scales and difficulty in sourcing the required data from the original authors. The inability to acquire missing data from all eligible

studies was not unexpected and an understood part of the meta-analysis process. However, missing data and a small sample size limited evidence synthesis and the meta-analysis to some extent. Despite these limitations, this study considerably enriched our understanding of the association between PHPT and metabolic disorders by demonstrating that PHPT patients had obesity, impaired glucose tolerance and insulin resistance.

In conclusion, compared with healthy controls, PHPT patients had greater insulin resistance, but only hypercalcemia PHPT patients had higher FBG. There was no significant difference in BMI between PHPT patients and healthy controls.

## Disclosure of conflict of interest

None.

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