Meta-analysis on the effect of mild primary hyperparathyroidism and parathyroidectomy upon arterial stiffness

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Disclosure summary: The authors have nothing to disclose

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Abstract

Context: current data about the cardiovascular manifestations of mild primary hyperparathyroidism (pHPT) are often conflicting. Pulse wave velocity (PWV) is the gold-standard method for assessing aortic stiffness, which predicts cardiovascular morbidity and mortality.

Objective: Primary outcomes were to investigate if mild pHPT was associated with higher PWV and if parathyroidectomy (PTX) reduced PWV in mild pHPT. Secondary outcome was to investigate blood pressure changes after PTX.

Data sources: PubMed, Google Scholar, SCOPUS, Web of Science, and the Cochrane Library

Study selection: Eligible studies included reports of PWV in patients with mild pHPT and controls, or in patients with mild pHPT before and after PTX.

Data extraction: Two investigators independently identified eligible studies and extracted data. Pooled mean difference (MD) was the summary effect measure. Data were presented in forest plots with outlier and influential case diagnostics.

Data synthesis: Nine observational studies and one RCT were selected, including 433 patients with mild pHPT, 171 of whom underwent PTX, and 407 controls. PWV was significantly higher in mild pHPT as compared to controls (MD=1.18, 0.67 to 1.68, $p<0.0001$). Seven studies evaluated the effect of PTX on PWV. PTX significantly reduced PWV (MD= -0.48, -0.88 to -0.07, $p=0.022$).

Conclusion: Aortic stiffness is increased in patients with mild pHPT, supporting the notion that also mild pHPT is associated with adverse cardiovascular manifestations. PTX significantly reduced arterial stiffness in mild pHPT, indicating that the benefit of PTX over cardiovascular manifestations should not be dismissed but it deserves further studies.

Keywords: hyperparathyroidism, PTH, arterial stiffness, pulse wave velocity, PWV, meta-analysis, outlier and influence diagnostics

Introduction

Primary hyperparathyroidism (pHPT) is one of the most common endocrine disorders, especially in female gender, affecting between 0.4% and 11% of the population, where the highest rates are due to patients with normocalcemic pHPT (1). This disorder is due to the autonomous secretion of parathyroid hormone (PTH) by one or more parathyroid glands. Inappropriately high PTH levels lead to a symptomatic disease characterized by hypercalcemia, kidney stones and over skeletal disease with high risk of fractures. Nowadays, however, pHPT is diagnosed most of the times incidentally, in patients who are almost asymptomatic and exhibit normal or only mildly elevated calcium levels (2). In these patients, parathyroidectomy (PTX) has been found effective in increasing bone mineral density (3-6) and in preventing kidney stone disease (7), such that signs of bone or renal damage represent current indications to PTX in mild pHPT (2). By contrast, current data about the cardiovascular manifestations of mild pHPT are often conflicting and available randomized studies on this topic showed no cardiovascular benefit of PTX in mild pHPT (8-10). As a consequence, signs of cardiovascular damage are not included in current guidelines on mild pHPT management (2).

Nevertheless, in a recent meta-analysis, PTX was found effective in reducing left ventricular hypertrophy, and the greatest benefit was observed in patients with the highest baseline PTH values, rather than calcium (11). Interestingly, mild pHPT was found associated also with coronary microvascular dysfunction, which was restored after PTX (12). These findings are consistent with a large body of evidence showing that PTH exerts direct actions on the cardiovascular system, including cardiac myocytes, as well as endothelial and vascular smooth muscle cells (VSMC), supporting a role for PTH in the development of cardiovascular disease (13).

Aortic stiffness is a useful and widely validated predictor for cardiovascular morbidity and mortality (14-16). The measurement of pulse wave velocity (PWV) is considered the gold-standard method for assessing arterial stiffness in the aorta (17, 18). Several studies have evaluated the effect of mild pHPT and PTX upon arterial stiffness by measuring PWV. The results of these investigations have been conflicting, but given that most studies were small, they might have lacked adequate statistical power to detect significant changes of PWV. The primary outcomes of this meta-analysis were to assess (i) whether patients with mild pHPT exhibited higher aortic stiffness than controls as assessed by PWV and (ii) whether parathyroidectomy reduced it. The secondary outcome was to assess whether PTX induced blood pressure changes.

Materials and methods

Data sources and search strategy

This systematic review and meta-analysis were conducted following the preferred reporting items for systematic reviews and meta-analyses PRISMA checklist (19). We conducted a systematic literature search on PubMed, Google Scholar, SCOPUS, Web of Science, and the Cochrane Library to select all the studies evaluating PWV in patients with pHPT as compared to controls or in patients with pHPT before and after parathyroidectomy. The query included the terms "hyperparathyroidism" or " PTH" combined with any of the following: "stiffness", "arterial", "aortic stiffness", "arterial compliance", "pulse wave velocity", "PWV" and "arterial elasticity". The search was last updated on October 4, 2020. Librarians helped retrieve full-text articles beyond electronically available published literature (20). We contacted authors for unpublished paired data when results were analyzed with the intention-to-treat-approach, with the last value carried forward in case of missing data (10).

Study selection

Studies were examined and selected for inclusion independently by two investigators (V.B. and L.Z) and a third one (S.B.) was consulted in case of controversy. Investigators were not blinded to authors, institutions, journals, or interventions while selecting studies. Inclusion criteria were as follows: (i) original studies; (ii) adult population; (iii) primary mild hyperparathyroidism; (iv) report of PWV as assessed by validated methods. In particular, consistent with the literature (21), we limited mild pHPT patients to those with serum calcium < 3 mmol/L (<12 mg/dL). Exclusion criteria of studies were as follows: (i) studies non written in English; (ii) wrong publication types (reviews, meta-analysis, study protocols, case reports, letters, errata, conference proceedings, book chapters); (iii) wrong population (i.e. pre-clinical studies or studies with secondary or tertiary hyperparathyroidism); (iv) wrong outcome (i.e. absence of PWV). Studies were also excluded if relevant information regarding the study design or outcomes was unclear or if there was any doubt regarding duplicate publications. At the end of our qualitative analysis, we identified 13 studies and excluded 3 of them from our quantitative analysis. Exclusion criteria of these studies were: (i) different design (22-24) and (ii) different measures of outcomes (i.e. PWV reported as quartiles rather than mean ± SD) (22, 23). The remaining 10 studies were selected for inclusion. **Figure 1** shows the stepwise procedure for study selection.

Data extraction and risk of bias assessment

Data on study design, patient characteristics, interventions, PWV measurement, and follow-up were extracted independently by two investigators (V.B. and S.B.). In order to assess the risk of bias of the included studies, we used the Cochrane Collaboration tool, namely the ROBINS-I (25) for the non-randomized trials. The ROBINS-I assesses seven domains of bias, specifically: (D1) bias due to confounding, (D2) bias due to selection of participants, (D3) bias in classification of interventions, (D4) bias due to deviation from intended intervention, (D5) bias due to missing data, (D6) bias in measurement of outcomes, and (D7) bias in selection of the reported result. For each of these risk domains of bias, the studies were categorized as having a low, moderate, serious or critical risk. If the domains were not applicable, the risk of bias assessment was reported as not applicable (NA). Risk of bias was independently assessed by SB and VB and disagreements were resolved through discussion. Weighted bar and traffic-light plots of risk-of-bias assessment were designed using "robvis" R-package (26), as shown in **Figure 2**.

Statistical analysis

To investigate the difference of PWV between pHPT and controls (unpaired data) pooled MD was generated using the inverse-variance weighting method. In this case we chose MD as the summary effect measure because outcome measurements in all studies were made on the same scale. To investigate the difference of PWV, SBP and DBP in patients with pHPT before and after PTX (paired data), we calculated the mean change value from baseline to follow-up and we used the difference in the mean change value as the summary effect measure. When standard deviation (SD) for the change score was not reported, we computed SD using the p-value for testing whether the follow-up score was significantly different from baseline. Only in two studies (Barletta et al. and Kosch et al.) the exact p-value was not available (ns): in this case we decided to use a value of p-value of 0.10. The Der-Simonian and Laird random-effect model was used for the analysis of heterogeneity, which accounts for intra and inter-study variability. Pooled data were presented in forest plots.

The degree of heterogeneity was assessed by the visual inspection of the forest plots and I-squared (I^2) statistic with its 95% confidence intervals. Heterogeneity was considered low for I^2 values less than 25–50%, moderate for 50–75%, and high for ≥ 75%.

In addition, in order to identify potential outliers and influential cases that might distort and affect the validity of the meta-analysis, we explored effect sizes and heterogeneity with the outlier and influential case diagnostics (including the Baujat plot, influence analysis and leave-one-out-method). When the number of studies/comparisons was ≥ 10 entries, heterogeneity was evaluated with the

Baujat plot, which is a graphical method to describe heterogeneity (27). Otherwise, outliers and influential cases were identified with the influence analysis and the influence diagnostic plots (28). The influence analysis is based on the impact of excluding studies on various statistics such as the summary externally standardized residuals, DFFITS values, Cook's distances, covariance ratios, leave-one-out estimates of the amount of heterogeneity (tau-squared), leave-one-out estimates of the test statistics for heterogeneity (Q), hat values, and weights (28). The most important ones are the DIFFTS value, the cook's distance, and the covariance ratio. As a rule of thumb, influential cases are studies with extreme values (respect to a proposed cut-off) in the graphs and they are displayed in red color. Then, to assess the stability of the pooled results, we performed a sensitivity analysis by sequential omission of individual studies with the leave-one-out-method. This method allows to detect more easily the studies that influence the overall estimate of a meta-analysis, and to assess if this influence may distort the pooled effect (28). Finally, based on this outlier and influential case diagnostics, the meta-analytic models were run both with and without outliers/influential studies.

Publication bias was visually described by funnel plot while Egger 's test and Begg 's test were performed to evaluate the symmetry of funnel plots (29): this analysis was not performed when there were less than ten comparisons because of insufficient power to distinguish chance from real asymmetry. Data were analyzed using the R statistical software (version 4.0.2-packages: meta, metafor, dmetar). A two-tailed P-value <0.05 was considered statistically significant.

Results

Study characteristics

Ten studies, 9 non-randomized studies and 1 randomized clinical trial (RCT), were included in this meta-analysis (10, 20, 30-37), and their characteristics are shown in **Tables 1-2.** These studies were published between 2000 and 2020. All the non-randomized studies reported PWV mean results (m/s) in patients with mild pHPT (n= 393) as compared to controls (n=407), as shown in **Table 1**. In three of them, patients with mild pHPT were divided into two subgroups based on calcium and blood pressure (31, 33, 36). Six non-randomized studies and the RCT included paired analyses, reporting PWV (m/s) in patients with mild pHPT before (n=171) and after surgery (n=160) (**Table 2**). Overall, patients with mild pHPT had calcium < 3 mmol/L (<12 mg/dL). Mean age of study participants ranged from 45 to 68 years. They were predominantly female (62-100%), and overweight in all but two studies (20, 34).

Looking at the participant selection in case-control studies (**Table 1**), patients were generally matched by age, sex, BMI, and other cardiovascular risk factors, such as smoking habit, blood pressure, glycemia, lipid profile, and creatinine levels. Two studies did not provide data on smoking habit (30, 37) and one study did not provide data on BMI, glucose and lipid levels (30). Tordjman et al. included a minority of patients with impaired glucose metabolism (31), and Buyuksimsek et al. patients with mild hypertension (37).

Looking at the paired analyses on PWV before and after PTX, follow-up was scheduled within 12 months from PTX (**Table 2**). A total of 171 patients underwent PTX, but follow-up data were available for 160 patients (93.6%). In the study by Barletta et al., 14 patients were operated on and 10 were seen at 6-month follow-up (30). In the intervention group of the RCT by Ejlsmark-Svensson et al., 40 patients were operated on and 33 were seen at 3-month follow-up (10). In this case (10), unpublished changes in PWV and blood pressure (mean ± SE) with no data carried forward were obtained from the corresponding author.

PWV was assessed by carotid-femoral applanation tonometry with the use of 80% direct carotid-femoral distance, except for three studies. Barletta et al. used piezoelectric transducers to record brachial and radial pulse tracings (30), Cansu et al. used brachial pulse wave analysis to detect aortic PWV (36), and Buyuksimsek et al. measured carotid-femoral PWV based on Doppler ultrasound examination with the distance calculated by subtractive method (37).

Figure 2 shows the risk of bias assessment. Overall, the majority of the studies that were evaluated showed a low risk of bias.

Meta-analysis

First, we compared PWV in patients with mild pHPT to controls (CNT). The pooled MD of PWV was 1.18 [0.67; 1.68], p-value < 0.0001, indicating that the absolute difference between the mean values of PWV in the two groups was significant, and patients with mild pHPT had significantly higher arterial stiffness than CNT (**Figure 3**). The I^2 statistic indicated significant heterogeneity (I^2=74.1%, uncertainty range 54.2-85.4%, p<0.0001). To detect the main studies contributing to the heterogeneity of the meta-analysis, we used the Baujat Plot as well as the influence analysis, showing that only the study by Buyuksimsek et al. (37) could affect the pooled MD result, possibly due to its sample size and the inclusion of participants with hypertension. Nevertheless, the leave-one-out-method showed that even when this study was removed, the pooled MD remained significant (MD=1.00 [0.60; 1.40], p<0.0001), with a reduction of the heterogeneity of the meta-analysis (I^2=52.1%). The funnel plot for

the effect of mild pHPT on PWV suggested no publication bias, which was confirmed by Egger's (t=0.14; p=0.89) and Begg's (t=0.69, p=0.49) tests.

Second, based on the seven studies with paired analyses, we evaluated if PTX was associated with a reduction of PWV. Overall, the pooled analysis showed that MD was -0.48 [-0.88; -0.07], p=0.022 (**Figure 4A**). The I^2 statistic indicated significant heterogeneity (I^2=83.4%, uncertainty range 67.2-91.6%, p<0.0001). Interestingly, the influence analysis showed that there was no study to consider as an outlier or an influential case that should be removed (**Figure 4B**).

Third, we analyzed if PTX was associated with a change in SBP and DBP. With respect to SBP, the overall MD was -2.47 [-4.73; -0.20], p=0.033 (**Figure 5A**). The I^2 statistic indicated significant heterogeneity (I^2=78.3%, uncertainty range 55.1-89.5%, p-value<0.0001). The visual inspection of the forest plot and the influence analysis showed that the study contributing most to the heterogeneity of the meta-analysis was that of Rosa et al. (**Figure 5B**), which was due to a particularly strong reduction in SBP. The leave-one-out-method showed that the overall MD changed by omitting the study by Rosa et al. (MD= -1.61 [-362; 0.40], p=0.12), indicating that this study was significantly affecting our pooled results and it should be removed. In this case, the meta-analytic model was run without this study, showing that PTX did not significantly change SBP (**Figure 5C**). With respect to diastolic blood pressure, the overall MD was not significant.

Discussion

Patients with symptomatic pHPT have an excess risk of mortality from cardiovascular disease, which is gradually reduced after surgery, as shown by observational cohort studies (38, 39). In this setting, operation at early disease stages may offer a survival advantage (40). It has been demonstrated that patients with pHPT exhibit vascular and myocardial calcifications, hypertension, left ventricular hypertrophy, which account for the risk of cardiovascular mortality (41). Nevertheless, this seems to be a feature of severe pHPT (42), while in case of mild pHPT the evidence for cardiovascular involvement appears to be conflicting.

Several studies have addressed the cardiac changes after PTX in mild pHPT. As reviewed in a recent meta-analysis (11), the studies including patients with higher calcium levels (43, 44) indicated more often a significant benefit of PTX upon left ventricular hypertrophy than those including patients with milder disease (9, 45-47), where surgery did not lead to a statistically significant benefit. In the study of Persson et al., 49 patients with mild pHPT were randomized to observation or PTX. After two years, ecocardiography revealed only a borderline effect of PTX on left ventricular mass, and a significant 11% reduction in diastolic dimension of the interventricular septum (9). Walker et al. studied the 2-year effects of PTX in 44 patients with mild pHPT, reporting that carotid plaque and left

ventricular mass did not change after PTX (47). Nevertheless, in this study, PTX reduced carotid stiffness by 28% in patients with preexisting cardiovascular abnormalities (47).

Arterial stiffness refers to the loss of elastic properties of the arterial wall, it reflects ageing of the cardiovascular system (18, 48), and it has independent predictive value for cardiovascular disease morbidity and mortality (14, 49). Arterial stiffness can be assessed by several methods, among which carotid-femoral PWV is currently the recommended one for non-invasively estimating the stiffness of the aorta (17, 18), and it is usually measured by applanation tonometry or other validated devices that can measure the speed at which the pulse wave travels in the vessel (50). Aortic stiffness as measured by PWV allows to reclassify cardiovascular risk in several clinical situations (14) and it seems to be particularly useful in patients at intermediate risk as well as in patients without standard cardiovascular risk factors (15, 51). Thus, it may be suitable in special populations that have an increased cardiovascular risk, such as patients with pHPT.

PTH has been found associated with arterial stiffness in the general population (22, 23). To date, only a few studies have evaluated arterial stiffness parameters in patients with mild pHPT with conflicting results. Some of these works show that patients with mild pHPT exhibit an increased augmentation index (21, 52), which is positively correlated to PTH. To our knowledge, this is the first meta-analysis to assess PWV in patients with mild pHPT as compared to controls, as well as before and after PTX. Our meta-analysis shows that mild pHPT was associated with higher arterial stiffness, as compared to controls, and that PTX significantly reduced it. Interestingly, the outlier and influential case diagnostics showed that in the unpaired analyses, the study by Buyukimsek et al. was an outlier, but the overall MD remained significant even when we removed it, while the overall MD of PWV before and after PTX was not influenced by any particular study. The benefit of PTX was observed in the studies with a follow-up of 6 months, and this is in line with the results of a meta-analysis by McMahon showing that PTX significantly reduced left ventricular hypertrophy and the benefit was observed in the studies with a follow-up of 6 months (11). Nevertheless, whether a reduction of PWV could translate in a possible reduction of cardiovascular outcomes is yet to be determined in long-term studies.

Our secondary outcome was to assess blood pressure changes after PTX in the selected studies. Although in our meta-analysis PTX seemed to reduce also SBP, this result was primarily due to the study by Rosa et al., who found a strong reduction of SBP, which was lowered by 8 mmHg after PTX, an for this reason was an outlier. When we removed this study, PTX did not significantly change SBP. In the literature, pHPT is often associated with hypertension, but PTX is not invariably associated with blood pressure improvement (53). Studies with ambulatory monitoring of blood pressure showed that the prevalence of hypertension in patients with mild pHPT was 47%, which is higher than in the general population (54). In addition, patients with mild pHPT exhibited more frequently a non-

dipping pattern (54), and an increased systolic blood pressure variability (55), which are considered additional cardiovascular risk factors. Although it has been found that PTX significantly reduced blood pressure levels in hypertensive patients with mild pHPT (56), in recent RCT, PTX did not ameliorate blood pressure as compared to observation (8-10).

Nevertheless, our meta-analysis on PWV indicates that mild pHPT increases aortic stiffness, which is reduced by PTX. This is in line with the concept that prolonged PTH excess affects the vascular system, leading to its dysfunction or structural changes. A few mechanisms might explain PTH-induced arterial remodeling. On one hand, PTH has direct tissue actions on both endothelial and VSMC (53). For instance, PTH stimulates endothelial nitric oxide synthase (57), which contributes to vascular injury through reactive oxygen species generation when there is an excess production of superoxide (58). It induces the expression of other tissue mediators of vascular injury, such as IL-6, RAGE and VEGF (59, 60). It may exert also an ionoforic effect leading to intracellular calcium overaload. For instance, patients with mild pHPT exhibited increased intracellular calcium concentrations in platelets (61), suggesting that there might be an abnormal calcium metabolism also at the level of VSMC, leading to increased peripheral vascular resistance. On the other hand, PTH has also systemic actions, as it was found to promote the activity of the renin-angiotensin-aldosterone system, as well as the activity of the sympatethic nervous system, contributing to arterial remodeling and cardiovascular disease (62).

Strengths and limitations. The limitations of this meta-analysis include the fact that the majority of the studies were small, non-randomized and only a few of them evaluated the effects of PTX on PWV. In addition, in these studies, PWV was assessed not only with applanation tonometry but also with mechanotransducers, Doppler ultrasounds and oscillometric methods, which increases the risk of bias in outcome measurement. Nevertheless, only validated methods able to provide reliable aortic PWV values were considered. By contrast, the strengths of our meta-analysis include the choice of PWV to measure arterial stiffness, which is in line with current recommendations, and the use of outlier and influential case diagnostics. This diagnostics showed that our data on PWV were not due to outlying studies.

In conclusion, our meta-analysis shows that mild pHPT is associated with higher aortic stiffness, which is reduced by PTX. These data suggest that operating patients with mild pHPT could improve their aortic stiffness, whereby PTX might reduce their cardiovascular risk. Therefore, we believe that the issue of cardiovascular involvement in mild pHPT, and its reversal after PTX, should not be dismissed. Further randomized studies, on larger cohorts and different subgroups of patients with mild pHPT, are needed to confirm our findings and identify the patients who might benefit from PTX in terms of cardiovascular risk.

Acknowledgements

We thank Dr Henriette Ejlsmark-Svensson for providing unpublished data

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Funding statement: This work did not receive specific funding support

Data availability statement: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figure legend

Figure 1. Stepwise procedure for study selection.

Figure 2. Risk of bias assessment. (A) Description of bias assessment in every study included. The overall risk of bias of Barletta et al. was judged serious due to: (i) lack of data on smoking habit, BMI, glucose, and lipids; (ii) missing data of 4 patients who underwent PTX; (iii) method of measuring PWV. The overall risk of bias of Buyuksimsek et al. judged moderate due to: (i) lack of data on smoking habit; (ii) selection of participants with hypertension; (iii) method of measuring PWV. Otherwise, we took into account that Tordjman et al. and Ejlsmark-Svensson et al. included patients with impaired glucose metabolism, Cansu et al. measured PWV with brachial pulse wave analysis.

Figure 3. PWV in patients with mild pHPT vs CNT. Forest plot indicating the effect of mild pHPT on PWV as compared to CNT. TE is for estimate of treatment effect; SE is for standard error of treatment estimate.

Figure 4. Impact of surgery on PWV. (A) Forest plot indicating the effect of PTX on PWV in patients with mild pHPT. TE is for estimate of treatment effect; SE is for standard error of treatment estimate. (B) Influence analysis of the studies evaluating the effects of PTX on PWV. Outliers and influential cases are displayed in red color. Bar is for Barletta et al., Can is for Cansu et al., Ejl is for Ejlsmark-Svensson et al, Kos is for Kosh et al., Rin is for Ring et al., Ros is for Rosa et al, Sch is for Schillaci et al.

Figure 5. Impact of surgery on SBP. (A) Forest plot indicating the effect of PTX on SBP in patients with mild pHPT. TE is for estimate of treatment effect; SE is for standard error of treatment estimate. (B) Influence analysis of the studies evaluating the effects of PTX on SBP. Outliers and influential cases are displayed in red color. Bar is for Barletta et al., Can is for Cansu et al., Ejl is for Ejlsmark-Svensson et al, Kos is for Kosh et al., Rin is for Ring et al., Ros is for Rosa et al, Sch is for Schillaci et al. (C) Forest plot indicating the effect of PTX on SBP in patients with mild pHPT after omitting influential studies.

Table 1. Characteristics of patients recruited in observational case-control studies

Study	N°of pts		Age (years)		Sex (%F)		BMI (Kg/m²)		Calcium (mmol/L)		SBP (mmHg)		DBP (mmHg)		PWV (m/s)	
	pHPT	*CNT*	*pHPT*	*CNT*	*pHPT*	*CNT*	*pHPT*	*CNT*	*pHPT*	*CNT*	*pHPT*	*CNT*	*pHPT*	*CNT*	*pHPT*	*CNT*
Barletta G 2000	14	20	60±11	60±8	86%	85%	-	-	2.88±0.26	2.37±0.18	136±10	135±9	77±7	76±5	8.8±1.6	8.2±3.5
Kosch M 2001	20	20	45±5	46±3	65%	65%	23.4±3.6	23.0±3	2.9±0.05	2.4±0.02	128±4	125±2	78±2	77±2	9.9±0.7	10±0.6
Tordjman KM (1 NC) 2010	13	25	65±8	66±9	85%	80%	27.5±5.2	27.2±5.7	2.39±0.09	2.29±0.09	136±20	137±18	74±8	72±8	8.4±1.3	8±1.2
Tordjman KM (2 HC) 2010	12	25	68±11	66±9	75%	80%	26.9±4	27.2±5.7	2.76±0.07	2.29±0.09	142±25	137±18	76±9	72±8	8.4±1.2	8±1.2
Schillaci G 2011	24	48	56±10	56±7	62%	62%	27.3±3	27.2±3	2.74±0.2	2.37±0.1	136±14	135±15	85±9	84±8	11.4±2	9.6±2
Rosa J (1 NT) 2011	16	18	52±14	48±15	100%	100%	24.6±3.4	25.3±3.8	2.73±0.15	2.34±0.11	120±16	118±4	75±9	68±8	7.6±1.8	5.8±0.9
Rosa J (2 HT) 2011	28	28	65±10	63±10	100%	100%	28.3±4.7	27.4±4.8	2.81±0.22	2.35±0.14	136±17	135±19	77±10	74±10	10.1±2.5	8.5±2
Ring M 2012	48	48	54±9	55±9	73%	73%	24±3	23.5±2.1	2.61±0.12	2.29±0.08	126±16	119±13	80±8	76±8	8.7±1.5	8.1±1.6
Stamatelopoulos K 2014	102	102	61±8	61±7	100%	100%	27.4±4.5	25.5±3.5	2.69±0.22	2.37±0.12	130±23	121±18	79±14	73±9	9.1±2.3	8.6±2.1
Cansu GB (1 NC) 2016	16	15	58±7	53±4	100%	100%	28.7±4.6	27.5±3.9	2.30±0.10	2.27±0.07	131±13	117±14	72±9	73±12	9.3±1.2	7.8±0.8
Cansu GB (2 HC) 2016	17	15	51±8	53±4	100%	100%	28.1±3.7	27.5±3.9	2.73±0.17	2.27±0.07	129±15	117±14	73±10	70±8	9.6±1.8	7.8±0.8
Buyuksimsek M 2020	83	83	52±16	54±12	67%	67%	27.9±2.9	27.5±4.7	2.91±0.26	2.15±0.23	151±14	149±15	91±10	91±10	11.2±2.9	8.5±1.7

Data are mean ± SD values apart from in the study by Kosch et al. where data are mean ± SE values. pHPT is for primary hyperparathyroidism, CNT is for control, BMI is for body mass index, SBP is for systolic blood pressure, DBP is for diastolic blood pressure, PWV is for pulse wave velocity, NC is for normal calcium, HC is for high calcium, NT is for normotensive, HT is for hypertensive.

Table 2. Characteristics of patients included in case-crossover analyses

Study	N° of pts		Age (yrs)	Sex %F	BMI (kg/m²)		Calcium (mmol/L)		SBP (mmHg)		DBP (mmHg)		PWV (m/s)		Time to follow-up (months)
	Before	After			Before	After	Before	After	Before	After	Before	After	Before	After	
Barletta G 2000	14	10	60±11	100%	-	-	2.89±0.36	2.30±0.09	137±10	138±10	77±7	78±8	9±1.5	10±4.4	6
Kosch M 2001	20	20	45±5	65%	23.4±3.6	-	2.9±0.05	2.3±0.05	128±4	126±5	78±2	76±5	9.9±0.7	9.6±0.8	6
Schillaci G 2011	17	17	57±10	64%	27.3±3	27.1±3	2.77±0.2	2.25±0.1	134±15	131±14	83±10	83±10	10.9±2	9.8±2	1
Rosa J 2011	15	15	63±12	100%	27.2±4.7	27.3±4.8	2.82±0.23	2.14±0.23	131±20	123±18	75±13	75±11	9.05±1.8	8.54±1.8	6
Ring M 2012	48	48	54±9	73%	24±3	24.7±3.3	2.61±0.12	2.27±0.08	126±16	123±15	80±9	78±8	8.68±1.5	8.61±1.4	12
Cansu GB 2016	17	17	51±8	100%	28.1±3.7	27.5±3.9	2.73±0.17	2.23±0.07	129±15	124±14	82±9	78±9	9.6±0.8	8.4±1.5	6
Ejlsmark Svensson H 2019	40	33	62 (56-68)	73%	27 (23-31)	-	1.42 (1.39-1.47)	-	132±19	-	75±11	-	8.9±2	-	3

Data are mean ± SD values apart from in the study by Kosch et al where data are mean ± SE and by Ejlsmark-Svensson et al. where data are median (min-max). BMI is for body mass index, SBP is for systolic blood pressure, DBP is for diastolic blood pressure, PWV is for pulse wave velocity.

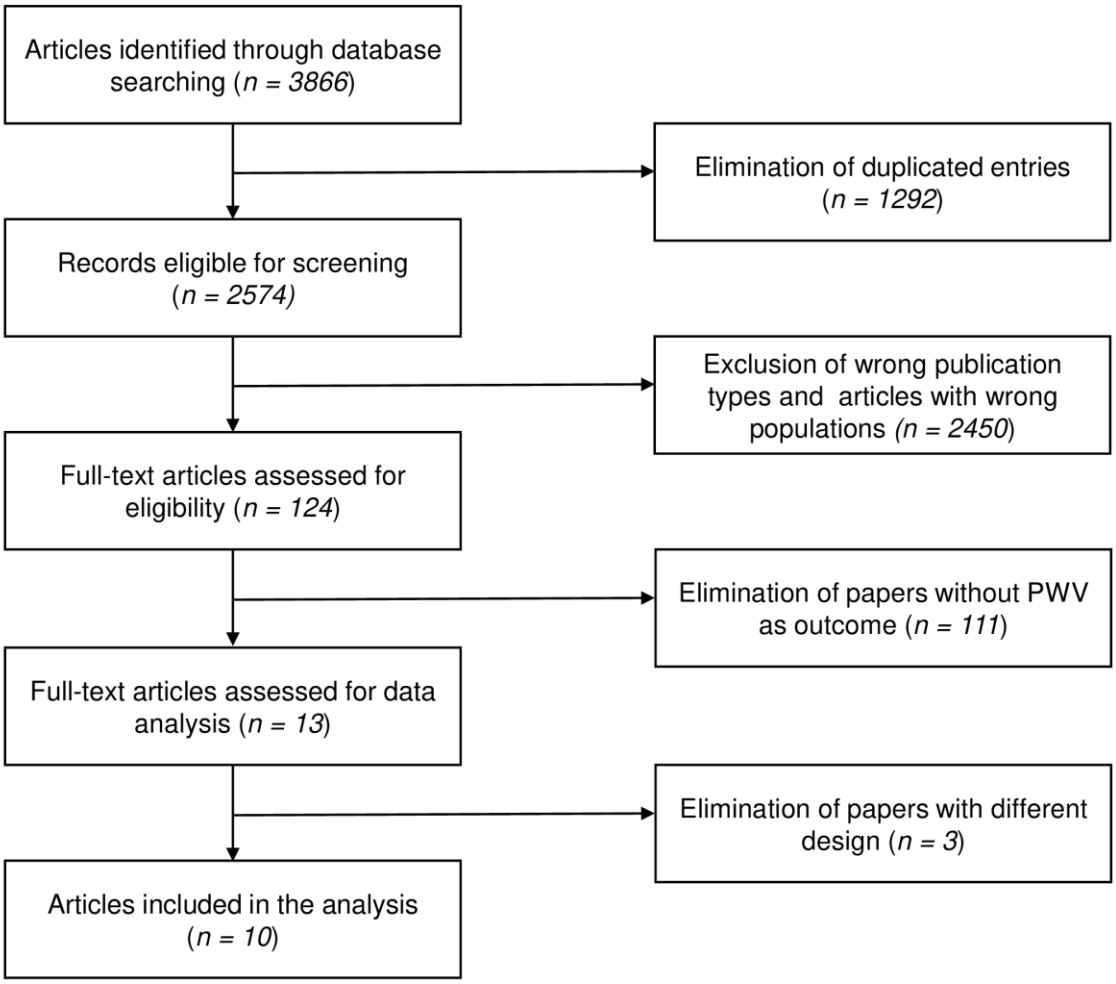


Figure 1

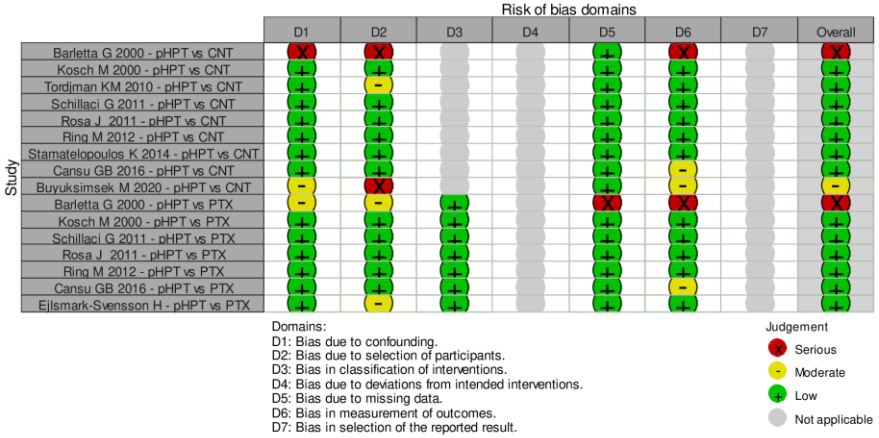
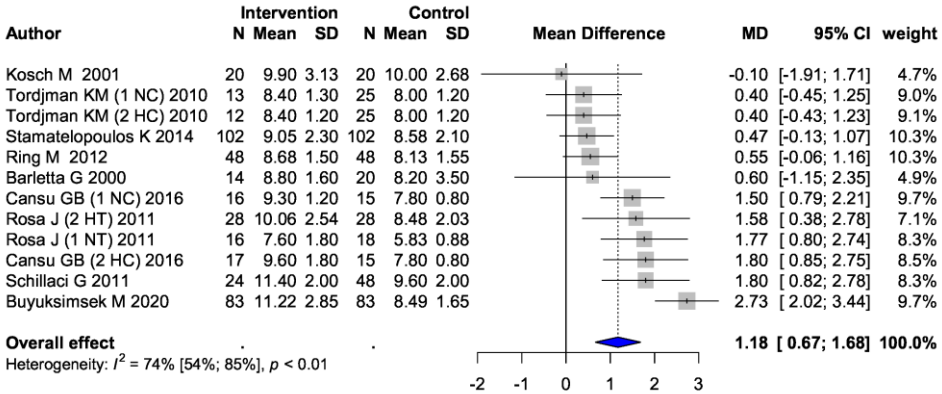


Figure 2

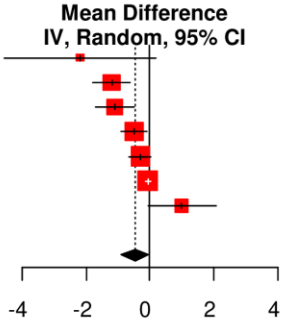
Figure 3



A

Study	TE	SE	Weight	Mean Difference IV, Random, 95% CI
Ejlsmark-Svensson H 2019	-2.18	1.2100	2.6%	-2.18 [-4.55; 0.19]
Cansu GB 2016	-1.20	0.2989	15.1%	-1.20 [-1.79; -0.61]
Schillaci G 2011	-1.10	0.3148	14.6%	-1.10 [-1.72; -0.48]
Rosa J 2011	-0.51	0.2015	18.2%	-0.51 [-0.90; -0.12]
Kosch M 2001	-0.30	0.1735	19.0%	-0.30 [-0.64; 0.04]
Ring M 2012	-0.07	0.0411	21.8%	-0.07 [-0.15; 0.01]
Barletta G 2000	1.00	0.5455	8.7%	1.00 [-0.07; 2.07]
Total (95% CI)			**100.0%**	**-0.48 [-0.88; -0.07]**

Heterogeneity: $Tau^2 = 0.1966$; $Chi^2 = 36.12$, df = 6(P < 0.01); $I^2 = 83\%$



B

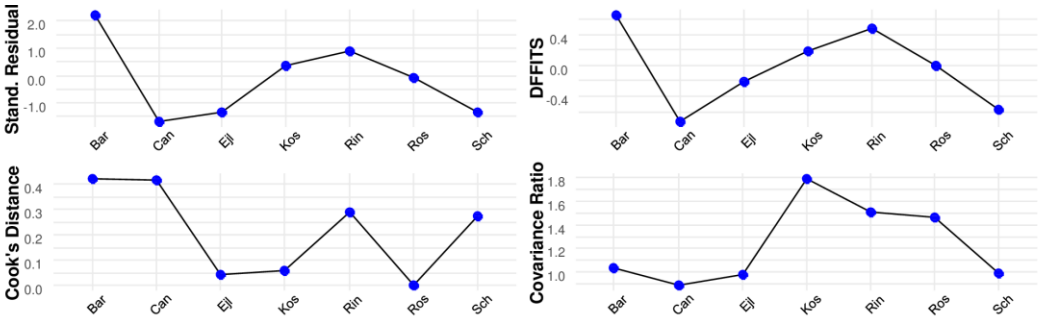


Figure 4

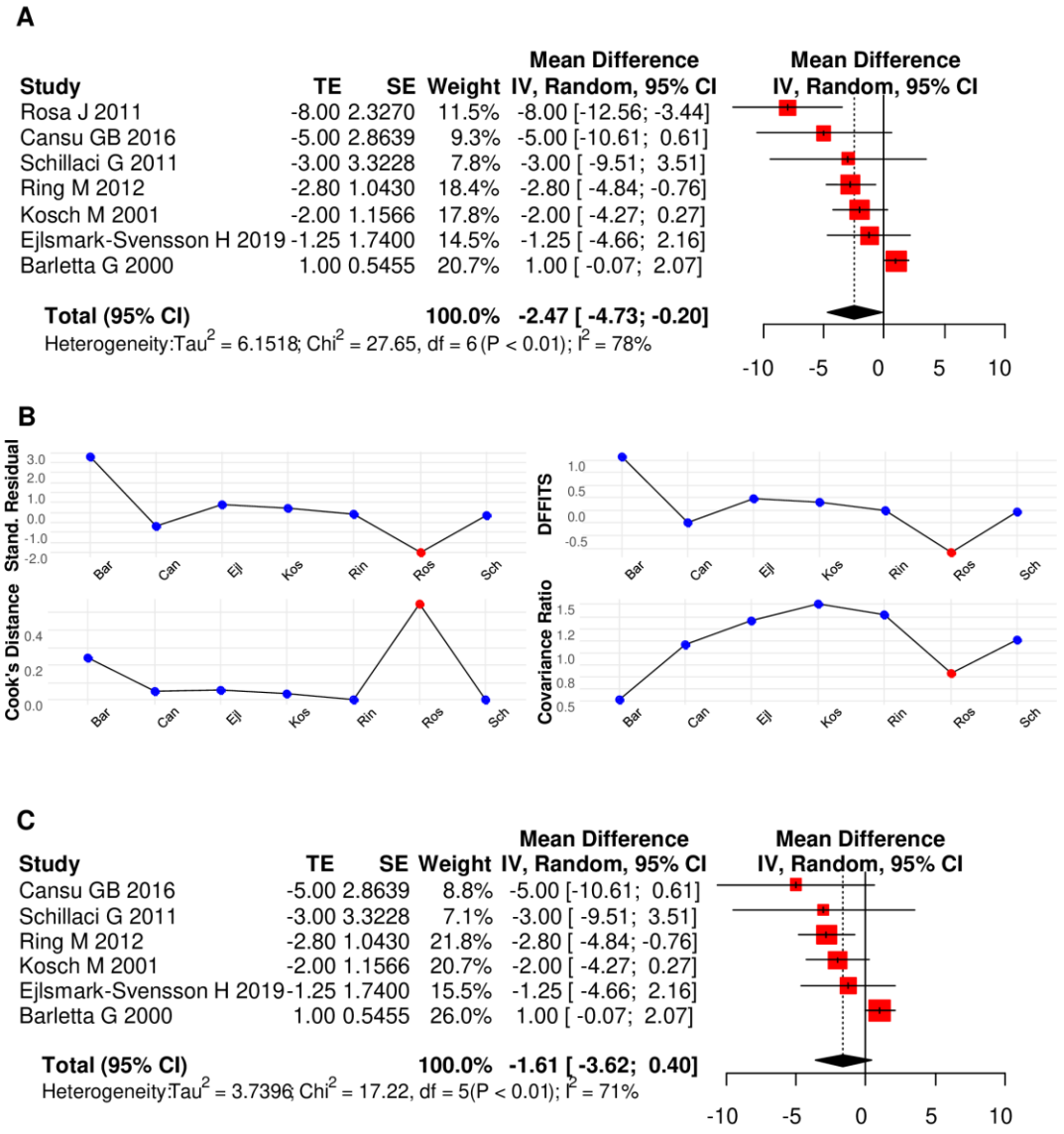


Figure 5