#### Check for updates

#### **OPEN ACCESS**

EDITED BY Elzbieta Skowrońska-Jóźwiak, Medical University of Łódź, Poland

#### REVIEWED BY Guido Zavatta, University of Bologna, Italy Krzysztof Cezary Lewandowski, Medical University of Lodz, Poland

\*CORRESPONDENCE Zhaohui Lyu metabolism301@126.com

#### SPECIALTY SECTION

This article was submitted to Bone Research, a section of the journal Frontiers in Endocrinology

RECEIVED 25 August 2022 ACCEPTED 17 October 2022 PUBLISHED 31 October 2022

#### CITATION

Wang A, Wang Y, Liu H, Hu X, Li J, Xu H, Nie Z, Zhang L and Lyu Z (2022) Bone and mineral metabolism in patients with primary aldosteronism: A systematic review and meta-analysis. *Front. Endocrinol.* 13:1027841. doi: 10.3389/fendo.2022.1027841

#### COPYRIGHT

© 2022 Wang, Wang, Liu, Hu, Li, Xu, Nie, Zhang and Lyu. This is an openaccess article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

# Bone and mineral metabolism in patients with primary aldosteronism: A systematic review and meta-analysis

Anning Wang<sup>1,2</sup>, Yuhan Wang<sup>1</sup>, Hongzhou Liu<sup>3</sup>, Xiaodong Hu<sup>1</sup>, Jiefei Li<sup>4</sup>, Huaijin Xu<sup>4</sup>, Zhimei Nie<sup>1</sup>, Lingjing Zhang<sup>4</sup> and Zhaohui Lyu<sup>2\*</sup>

<sup>1</sup>Medical School of Chinese PLA, Beijing, China, <sup>2</sup>Department of Endocrinology, The First Medical Center, Chinese PLA General Hospital, Beijing, China, <sup>3</sup>Department of Endocrinology, First Hospital of Handan City, Handan, Hebei, China, <sup>4</sup>Clinical Medical College, Nankai University, Tianjing, China

**Purpose:** Patients with primary aldosteronism (PA) tend to exhibit a high prevalence of osteoporosis (OP) that may vary by whether PA is unilateral or bilateral, and responsive to PA treatment. To explore relationships between bone metabolism, PA subtypes, and treatment outcomes, we performed a systematic review and meta-analysis.

**Methods:** The PubMed, Embase, and Cochrane databases were searched for clinical studies related to PA and bone metabolism markers. Articles that met the criteria were screened and included in the systematic review; the data were extracted after evaluating their quality. R software (ver. 2022-02-16, Intel Mac OS X 11.6.4) was used for the meta-analysis.

Results: A total of 28 articles were subjected to systematic review, of which 18 were included in the meta-analysis. We found that PA patients evidenced a lower serum calcium level (mean difference [MD] = -0.06 mmol/L, 95% confidence interval [CI]:  $-0.10 \sim -0.01$ ), a higher urine calcium level (MD = 1.29 mmol/24 h, 95% CI: 0.81 ~ 1.78), and a higher serum parathyroid hormone (PTH) level (MD = 2.16 pmol/L, 95% CI: 1.57 ~ 2.75) than did essential hypertension (EH) subjects. After medical treatment or adrenal surgery, PA patients exhibited a markedly increased serum calcium level (MD = -0.08 mmol/L, 95% CI:  $-0.11 \sim -0.05$ ), a decreased urine calcium level (MD = 1.72 mmol/24 h, 95% CI: 1.00 ~ 2.44), a decreased serum PTH level (MD = 2.67 pmol/L, 95% CI: 1.73 ~ 3.62), and an increased serum 25-hydroxyvitamin D (25-OHD) level (MD = -6.32 nmol/L, 95% CI:  $-11.94 \sim -0.70$ ). The meta-analysis showed that the ser um PTH level of unilateral PA patients was significantly higher than that of bilateral PA patients  $(MD = 0.93 \text{ pmol/L}, 95\% \text{ CI}: 0.36 \sim 1.49)$  and the serum 25-OHD lower than that of bilateral PA patients (MD = -4.68 nmol/L, 95% CI: -7.58 ~ 1.77). There were, however, no significant differences between PA and EH patients of 25-OHD, or BMD of femoral neck and lumbar spine. BMDs of the femoral neck or lumbar spine did not change significantly after treatment. The meta-analytical results were confirmed via sensitivity and subgroup analyses.

**Conclusion:** Excess aldosterone was associated with decreased serum calcium, elevated urinary calcium, and elevated PTH levels; these effects may be enhanced by low serum 25-OHD levels. The risks of OP and fracture might be elevated in PA patients, especially unilateral PA patients, but could be reduced after medical treatment or adrenal surgery. In view, however, of the lack of BMD changes, such hypothesis needs to be tested in further studies.

#### KEYWORDS

primary aldosteronism, osteoporosis, bone metabolism, secondary hyperparathy roidism (secHPT), meta-analysis

## Introduction

Osteoporosis (OP) is a common disease characterized by decreased bone mass and strength, and destruction of bone microstructure, increasing the fracture susceptibility. OP can be divided into primary and secondary OP. As secondary OP is considered to be reversible, it is important to identify the cause thereof. Secondary OP can develop in those with diseases of the endocrine and blood systems, and of connective tissue; after drug use; and for many other reasons, of which the use of glucocorticoids (1), (2) is the most common. Recently, the role played by mineralocorticoids in bone metabolism has become recognized; an increasing number of studies have shown that primary aldosteronism (PA) may cause secondary OP (3-5). In PA patients, the adrenal cortex autonomously secretes excessive amounts of aldosterone, resulting in sodium retention and potassium excretion, increased blood volume, and suppression of the activity of the renin-angiotensin-aldosterone system (RAAS). This manifests clinically as hypertension and hypokalemia, and is the most common cause of secondary hypertension. Previous studies have shown that PA can affect bone metabolism, and a bidirectional interaction may be in play between aldosterone and parathyroid hormone (PTH) (6, 7). Hence, this study aimed to explore the relationship between bone metabolism markers and the different subtypes of PA, and the effects of PA treatment through a systematic review and meta-analysis.

## Materials and methods

### Search strategy

The PubMed, Embase, and Cochrane databases were searched for clinical studies on PA and bone metabolism markers using the term "Hyperaldosteronism" in combination with "PTH, Calcium, BMD, Osteoporosis, and Secondary Hyperparathyroidism", with restrictions to the English language and human subjects; the databases were searched from their inceptions to March 6, 2022. We additionally searched the Grey Literature database. The above searches followed the PRISMA guidelines. All retrieved papers were imported into Zotero ver. 6.0.

## Selection criteria

Inclusion criteria: Randomized controlled trials; cohort, case-control, or observational studies. A PA diagnosis verified by at least one confirmatory test (a captopril challenge; a saline infusion, fludrocortisone suppression, or/and an oral sodium loading test); or *via* adrenal venous sampling (AVS). All studies reported the levels of blood parathyroid hormone (PTH), serum calcium and urinary calcium, serum 25-hydroxy vitamin D (25-OHD), serum alkaline phosphatase (AKP), and bone-specific alkaline phosphatase (BAP); the bone mineral density (BMD); and the prevalence or morbidity from OP, fractures, and hyperparathyroidism (HPT).

Exclusion criteria: The PA diagnosis was unclear or not specified. Clinical data were lacking. The experimental or case group, or cohort, were not PA patients. If PA subtypes were studied, there was no clear explanation as to how the subtypes were diagnosed.

### Data extraction and quality assessment

Two researchers independently conducted literature screening and data extraction using a standardized form while operating in a double-blinded manner. We extracted the first author names and countries, type of study, publication year, subject populations, interventions, basic clinical characteristics, bone metabolism markers (biochemical parameters and imaging indices), and follow-up data after PA treatment. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of casecontrol and cohort studies. Any disagreement between the two researchers was settled *via* discussion with, or arbitration by, a third specialist.

### Statistical analysis

R software (ver. 2022-02-16, Intel Mac OS X 11.6.4) (the "meta" package ver. 5.2-0) was used for statistical analysis. We calculated mean differences (MDs) between patients and controls (with 95% confidence limits [CIs]) for continuous variables, and odds ratios (ORs) with 95% CIs for dichotomous variables. We sought heterogeneity using the I<sup>2</sup> test, and considered that this was absent when  $I^2 < 50\%$ . If heterogeneity was absent, we used fixed-effect models for meta-analysis, but employed randomeffect models when heterogeneity was in play and the causes thereof were not discernible. Publication bias was assessed using the Egger's test; we also drew funnel plots during meta-analyses of at least 10 studies. Visual confirmation of funnel plot symmetry, or an Egger's test P-value > 0.05, indicated no publication bias. We performed sensitivity analysis on only "high quality" studies (NOS scores at least the median of all studies). We also performed subgroup analyses to explore the sources of heterogeneity.

## Results

### Search results

A total of 494 articles were retrieved, including 270 from PubMed, 215 from Embase, 9 from Cochrane, but none from the Grey Literature (Figure 1). After removing duplicate studies, reading the titles, and screening the full texts, 28 works were finally included in the systematic review (Table 1), of which 13 were newly included compared to a previous study (3). Eighteen articles were included in the meta-analysis. In detail, 12 studies (14, 17, 18, 21, 25-27, 29-33) compared 3,318 PA patients to 11,024 essential hypertension (EH) subjects in terms of the serum calcium and urinary calcium levels; the serum PTH, 25-OHD, and AKP levels; and the BMD. Twelve studies (17), (18), (25), (27, 29-31), (12, 15, 16, 28, 33) compared 501 PA patients before medical or surgical treatment to 491 who were followedup after treatment in terms of the serum calcium and urinary calcium levels; the serum PTH, 25-OHD, and BAP levels; and the BMD. Eight studies (nine datasets) (14), (25), (26), (29), (15), (11, 13, 19) compared 489 unilateral PA patients with 558 bilateral PA patients (three studies diagnosed PA via AVS after ACTH stimulation; four via AVS without ACTH stimulation; and one via AVS both with and without ACTH

stimulation); all presented the serum calcium and urinary calcium and PTH and 25-OHD levels; and the BMD.

## Quality assessment

Of the 28 included articles, 26 were case-control studies, one a cohort study, and one a descriptive study. The quality of the case-control studies is shown in Supplementary Table 3; the NOS score of the cohort study was 8. The NOS scores of all studies were at least 6 (median 8).

### PA vs. EH

Eight studies reported significantly lower serum calcium levels in PA than EH patients (MD = -0.06 mmol/L, 95% CI:  $-0.10 \sim -0.01$ ). The urinary calcium level was significantly higher in seven studies that compared PA patients to EH subjects (MD = 1.29 mmol/24 h, 95% CI:  $0.81 \sim 1.78$ ). Ten studies found that the serum PTH level was significantly higher in PA patients than in EH subjects (MD = 2.16 pmol/L, 95% CI:  $1.57 \sim 2.75$ ). While no significant differences were found between PA and EH patients on 25-OHD, on BMD of femoral neck and lumbar spine and on AKP (Figure 2).

# A comparison of data before and after treatment

Nine studies reported significantly higher serum calcium levels (MD = -0.08 mmol/L, 95% CI:  $-0.11 \sim -0.05$ ) after than before treatment of PA patients. The urinary calcium level was significantly lower after treatment (MD = 1.72 mmol/24 h, 95% CI:  $1.00 \sim 2.44$ ) in seven studies; the serum PTH level was significantly lower in 12 studies (MD = 2.67 pmol/L, 95% CI:  $1.73 \sim 3.62$ ); and the serum 25-OHD was significantly higher (MD = -6.32 nmol/L, 95% CI:  $-11.94 \sim -0.70$ ) in nine studies. None of the BAP level or the BMDs of the femoral neck or lumbar spine changed significantly after treatment (Figure 3).

## Unilateral vs. bilateral PA

The serum PTH level was significantly higher in unilateral than bilateral PA patients (MD = 0.93 pmol/L, 95% CI: 0.36 ~ 1.49) in eight studies (nine datasets). Six studies found that the serum 25-OHD level was significantly lower in unilateral than bilateral PA patients (MD = -4.68 nmol/L, 95% CI:  $-7.58 \sim -1.77$ ). However, no significant differences were found in terms of



TABLE 1 Characteristic of studies included in systematic review and meta-analysis.

Study	Design	Country	Patient and Control	Ν	age (year)	Male (%)	NOS scores
Zavatta, 2022 (8)	case-control	Italy	PA NFA	26 39	$58.00 \pm 8.90$ $59.00 \pm 8.80$	11 (42.3%) 17 (43.6%)	8
Tang, 2022 (9)	case-control	China	PA SA(GS+BS)	20 37	$38.80 \pm 10.10$ $36.10 \pm 14.60$	11 (55.0%) 19 (51.4%)	7
Liu, 2021 (10)	case-control	China	PA NFA	356 417	$50.00 \pm 11.00$ $51.00 \pm 12.00$	203 (57.0%) 219 (52.5%)	6
Kometani, 2021 (11)	case-control	Japan	(a) unilateral PA bilateral PA (without ACTH)	60 54	$52.00 \pm 12.00$ $52.00 \pm 12.00$	31 (51.7%) 27 (50.0%)	6
			(b) unilateral PA bilateral PA (with ACTH)	19 105	$55.00 \pm 11.00$ $51.00 \pm 11.00$	12 (63.2%) 52 (49.5%)	
Gravvanis, 2021 (12)	case-control	Greece	PA before treatment PA after treatment	63 63	60.00(31.00,78.00) 60.00(31.00,78.00)	37 (58.7%) 37 (58.7%)	8
Yokomoto, 2020 (13)	case-control	Japan	unilateral PA bilateral PA (with ACTH)	37 76	$56.00 \pm 14.00$ $54.00 \pm 11.00$	25 (67.6%) 23 (30.3%)	7
Tuersun, 2020 (14)	case-control	China	(a) PA EH	156 156	$49.86 \pm 8.72$ $48.99 \pm 8.60$	88 (56.4%) 88 (56.4%)	8
				76 80	49.11 ± 8.38 48.79 ± 8.86	43 (56.6%) 47 (58.8%)	

(Continued)

Study	Design	Country	Patient and Control	Ν	age (year)	Male (%)	NOS scores
			(b) unilateral PA bilateral PA (without ACTH)				
Asbach, 2020 (15)	case-control	German	(a) unilateral PA bilateral PA (with ACTH)	70 55	49.00(43.00,59.00) 45.00(41.00,53.00)	44 (62.9%) 35 (63.6%)	8
			(b) PA before treatment PA after treatment	60 60	-	38 (63.3%) 38 (63.3%)	
Adolf, 2020 (16)	case-control	German	(a) PA HS	36 18	59.00(53.00,64.00) 54.00(44.00,60.00)	0 (0%) 0 (0%)	8
			(b) PA before treatment PA after treatment	36 36	59.00(53.00,64.00) 59.00(53.00,64.00)	0 (0%) 0 (0%)	
Lenzini, 2019 (17)	case-control	Italy	(a) PA EH	42 63	$52.00 \pm 11.22$ $52.00 \pm 10.00$	24 (57.1%) 33 (52.4%)	7
			(b) unilateral PA bilateral PA	27 15	$52.00 \pm 11.00$ $52.00 \pm 12.00$	15 (55.6%) 9 (60.0%)	
			(c) PA before treatment PA after treatment	42 32	$52.00 \pm 11.22$ $52.00 \pm 11.02$	24 (57.1%)	
Loh, 2018 (18)	case-control	Malaysia	(a) PA EH	18 17	50.00(38.00,58.75) 50.00(38.50,61.50)	11 (61.1%) 11 (64.7%)	7
			(b) PA before treatment PA after treatment	15 15	-	-	
Lim, 2018 (19)	case-control	Korean	unilateral PA bilateral PA (with ACTH)	23 19	$46.50 \pm 11.50$ $51.50 \pm 9.80$	9 (39.1%) 12 (63.2%)	8
Kim, 2018 (5)	case-control	Korean	PA AI	72 335	$56.73 \pm 8.50$ $54.64 \pm 9.95$	-	8
Shu, 2018 (20)	case-control	China	OP OE HS	186 96 42	$59.60 \pm 4.35$ $58.70 \pm 4.40$ $58.60 \pm 4.90$	0 (0%) 0 (0%) 0 (0%)	8
Wu, 2017 (21)	cohort	China	PA EH	2533 10132	$50.55 \pm 14.57$ $50.69 \pm 17.90$	1176 (46.4%) 4708 (46.5%)	8
Salcuni, 2017 (22)	case-control	Italy	(a) PA non-PA	12 310	$60.40 \pm 13.50$ $61.10 \pm 9.30$	-	9
			(b) OP HS	213 109	-	-	
Notsu, 2017 (23)	case-control	Japan	PA HS	56 56	$58.70 \pm 11.10$ $59.40 \pm 11.50$	25 (44.6%) 25 (44.6%)	8
Zhang, 2016 (24)	case-control	China	PA NFA	84 58	$50.00 \pm 10.00$ $55.00 \pm 8.00$	44 (52.4%) 21 (36.2%)	6
Jiang, 2016 (25)	case-control	China	(a) PA EH	242 120	49.00(41.00,57.00) 50.00(42.00,58.00)	131 (54.1%) 53 (44.2%)	8
			(b) unilateral PA bilateral PA (without ACTH)	123 119	$46.57 \pm 11.33$ 52.70 ± 12.01	57 (46.3%) 74 (62.2%)	
			(c) PA before treatment PA after treatment	99 99	-	-	
Petramala, 2014 (26)	case-control	Italy	(a) PA EH HS	73 73 40	$52.50 \pm 11.20$ $55.60 \pm 12.40$ $55.70 \pm 6.10$	- -	6
			(b) unilateral PA bilateral PA (without ACTH)	35 38	$52.80 \pm 11.50$ $52.50 \pm 11.20$	-	
Ceccoli, 2013 (27)	case-control	Italy	(a) PA EH	116 110	$51.60 \pm 11.00$ $55.00 \pm 10.00$	65 (56.0%) 35 (31.8%)	7

(Continued)

Study	Design	Country	Patient and Control	Ν	age (year)	Male (%)	NOS scores
			(b) PA before treatment PA after treatment	40 40	-	-	
Salcuni, 2012 ( <mark>28</mark> )	case-control	Italy	(a) PA NFA	11 15	$56.00 \pm 9.30$ $56.70 \pm 9.50$	4 (36.4%) 5 (33.3%)	10
			(b) PA before treatment PA after treatment	9 9	-	-	
Rossi, 2012 (29)	case-control	Italy	(a) PA EH	58 74	$49.76 \pm 12.60$ $50.00 \pm 14.00$	-	9
			(b) unilateral PA bilateral PA (without ACTH)	46 12	$51.00 \pm 13.00$ $45.00 \pm 10.00$	-	
			(c) PA before treatment PA after treatment	46 46	$51.00 \pm 13.00$ $52.00 \pm 12.00$	-	
Pilz, 2012 (30)	case-control	German	(a) PA EH	10 182	$50.10 \pm 11.00$ $50.20 \pm 15.70$	4 (40.0%) 74 (40.7%)	9
			(b) PA before treatment PA after treatment	10 10	$50.10 \pm 11.00$ $51.20 \pm 11.50$	4 (40.0%) 4 (40.0%)	
Maniero, 2012 ( <mark>31</mark> )	case-control	Italy	(a) PA EH	44 61	$50.00 \pm 13.00$ $50.00 \pm 15.00$	18 (40.9%) 21 (34.4%)	9
			(b) PA before treatment PA after treatment	31 31	-	-	
Rossi, 1998 (32)	case-control	Italy	PA EH	16 16	$50.80 \pm 2.70$ $48.50 \pm 2.30$	8 (50.0%) 8 (50.0%)	7
Rossi, 1995 ( <mark>33</mark> )	case-control	Italy	(a) PA EH HS	10 20 10	$52.40 \pm 12.90 46.00 \pm 7.19 48.00 \pm 12.70$	5 (50.0%) 10 (50.0%) 5 (50.0%)	6
			(b) PA before treatment PA after treatment	14 14	-	-	
Lawrence, 1985 (34)	descriptive	American	PA	10	-	-	-

#### TABLE 1 Continued

N, number; NOS, Newcastle-Ottawa Scale; PA, primary aldosteronism; NFA, non-functioning adrenal tumour; SA, secondary aldosteronism; GS, gitelman syndrome; BS, bartter syndrome; AI, adrenal incidentaloma; OP, osteoporosis; OE, osteopenia; HS, healthy subjects.

the serum calcium or urinary calcium level or the BMDs of the femoral neck and lumbar spine (Figure 4).

## **Publication bias**

Publication bias in terms of PTH levels was sought in works that compared PA patients to EH subjects and PA patients before and after treatment. The funnel plots were substantially symmetrical, and the Egger's test revealed no obvious publication bias (Figure 5).

#### Sensitivity analysis

The median NOS score was 8. Thus, we repeated the analysis including only "high quality" studies (NOS  $\geq$  8). None of the AKP or BAP level, or the BMD, were included in sensitivity analysis because too few studies reported such data. After

excluding "low quality" studies, the above data on urinary calcium and serum PTH levels were largely confirmed. In contrast, no significant differences were found between PA patients and EH subjects in terms of serum calcium levels, or between PA patients before and after treatment in terms of serum 25-OHD levels. However, the serum calcium level differed significantly between unilateral and bilateral PA patients (Table 2).

#### Subgroup analysis

All of study location (Asia or Europe), the assays used to measure serum PTH and 25-OHD, and the AVS procedure (with or without ACTH stimulation) might have affected our assessments; we thus performed three subgroup analyses. At least one such analysis eliminated the heterogeneity, except in terms of the serum calcium, PTH, and 25-OHD comparisons between PA patients and EH subjects (Table 3).

$ \begin{array}{c c c c c c c c c c c c c c c c c c c $					PA			EH					
$ \frac{1}{1000} \frac{1}{1000} \frac{1}{1000} \frac{1}{10000} \frac{1}{10000} \frac{1}{100000} \frac{1}{1000000} \frac{1}{10000000000000000000000000000000000$		Study	Total	Mean	SD	Total	Mean	SD		Mean Difference	MD	95%-Cl	Weight
$ \frac{\log 2019}{\log 2019} + \frac{2}{2} + \frac{2}{2} + \frac{2}{2} + \frac{2}{2} + \frac{1}{2} + 1$		Tuersun 2020	156	2.31	0.1300	156	2.26	0.3000	_		0.05	[0.00; 0.10]	12.4%
$ \frac{\operatorname{Performula}{Prime} 2019}{\operatorname{Prime}} \frac{1}{10} + \frac{1}{20} + 20, 01000}{\operatorname{Prim}} \frac{1}{10} + \frac{1}{40} + 20, 0000}{\operatorname{Prim}} \frac{1}{10} + \frac{1}{40} +$		Jiang 2016	242	2.25	0.1000	120	2.23	0.1100			-0.06	[-0.08: -0.04]	14.2%
$ \frac{Cecccll 2013}{Present 196} if 196 422 2.01 is 100 if 10 428 0.0300 if 12 428 0.0100 if 12 428 0.0100 if 12 428 0.0100 if 12 428 0.0100 if 12 428 0.0000 if$		Petramala 2014	73	2.30	0.1000	73	2.42	0.0700		<b>-</b> ∃	-0.12	[-0.15; -0.09]	14.0%
$ \begin{array}{c} \operatorname{Ress} 2012 \\ \operatorname{Ress} 202 \\ \operatorname{Ress}$		Ceccoli 2013	116	4.45	0.1500	110	4.60	0.3000 -		-	-0.15	[-0.21; -0.09]	11.5%
$\frac{P_{12}}{P_{12}} \frac{P_{12}}{P_{12}} \frac{P_{12}}{$		Rossi 2012	58	2.32	0.1100	74	2.34	0.0900			-0.02	[-0.05; 0.01]	13.6%
$ \begin{array}{c} \text{constrained} 100 & 220 & 200 & 20 & 220 & 100 \\ \text{Performance} 100 & 200 & 20 & 220 & 100 \\ \text{Performance} 100 & 200 & 20 & 220 & 100 \\ \text{Performance} 100 & 200 & 20 & 220 & 100 \\ \text{Performance} 100 & 200 & 100 & 200 & 200 & 200 \\ \text{Performance} 100 & 200 & 100 & 200 & 200 & 200 \\ \text{Performance} 100 & 200 & 100 & 200 & 200 & 200 \\ \text{Performance} 100 & 200 & 100 & 200 & 200 & 100 & 200 & 200 \\ \text{Performance} 100 & 200 & 100 & 200 & 100 & 200 & 100 & 200 \\ \text{Performance} 100 & 200 & 100 & 200 & 100 & 200 & 100 & 200 & 100 & 200 \\ \text{Performance} 100 & 100 & 510 & 200 & 100 & 300 & 200 & 100 & 100 & 200 & 100 & 200 & 100 & 200 & 100 & 100 & 200 & 100 & 200 & 100 & 100 & 200 & 100 & 100 & 200 & 100 & 100 & 200 & 100 & 100 & 200 & 100 & 100 & 200 & 100 & 100 & 200 & 100 & 100 & 200 & 100 & 100 & 200 & 100 & 100 & 200 & 100 &$		Pliz 2012	10	2.26	0.1000	182	2.35	0.1000			-0.09	[-0.15; -0.03]	11.4%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Rossi 1995	10	2.23	0.0800	20	2.22	0.1100			0.01	[-0.06; 0.08]	11.0%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Random effects model Heterogeneity: $l^2 = 87\%$ , $\tau^2$	<b>683</b> <sup>2</sup> = 0.00	36, p <	0.01	752			[		-0.06	[-0.10; -0.01]	100.0%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	в							-0	).2 -	0.1 0 0.1 0	.2		
$ \frac{1}{12} $	Б	Study	Total	Mean	PA SD	Total	Mean	EH SD		Mean Difference	MD	95%-CI	Weight
$ \begin{array}{c} \begin{tabular}{ c c c c c c c c c c c c c c c c c c c$		Tuersun 2020	156	5.77	2.6400	156	5.03	2.3000			0.74	[ 0.19: 1.29]	18.4%
Pertamata 2014 73 6.07 2.9200 75 4.10 2.1000 Ross 2012 36 6.53 5.2200 74 8.53 2.8400 Ross 2012 86 6.53 5.200 74 8.53 2.8400 Ross 1938 16 5.04 0.800 16 3.53 2.8400 Ross 1938 16 5.04 0.810 15 4.43 3.200 17 2.78 2.9800 Ross 1938 16 5.00 5.040 16 3.33 2.2000 Ross 1938 16 5.00 5.040 16 3.33 2.2000 Ross 1938 16 5.00 5.040 16 3.33 2.2000 Ross 1938 16 5.00 5.040 16 3.32 2.2000 Ross 1938 16 5.00 5.040 16 3.22 2.0000 Lub 2018 18 2.429 2.2000 Ross 1938 16 5.00 5.040 16 3.22 2.0000 Ross 1938 16 5.00 5.040 16 3.22 8.20 3.070 Ross 1938 16 5.00 5.040 16 3.22 8.0000 Lub 2018 16 1.52 .575 100.05% Ross 1938 16 5.00 0.05 16 7.7 0.33 1.173 10.00% Ross 1938 16 5.00 0.05 16 7.7 0.33 1.173 10.00% Ross 1938 16 5.00 0.05 16 7.7 0.33 1.173 10.00% Ross 1938 16 5.00 0.05 16 7.7 0.33 1.173 10.00% Ross 1938 16 5.00 0.05 16 7.7 0.33 1.173 10.00% Ross 1938 16 5.00 0.05 16 7.7 0.00 17 0.083 0.170 Ross 1938 16 5.00 0.05 16 7.7 0.00 17 0.083 0.170 Ross 1938 16 5.00 0.05 16 7.7 0.00 17 0.083 0.170 Ross 1938 16 5.00 0.05 16 7.7 0.00 17 0.083 0.170 Ross 1938 16 5.00 0.05 16 7.7 0.00 17 0.083 0.170 Ross 1938 16 5.00 0.05 16 7.7 0.00 17 0.083 0.170 Ross 1938 16 0.000 17 0.083 0.170 Ross 1938 16 0.000 17 0.173 0.282 8.2700 Ross 1938 16 0.000 17 0.128 2.7000 Ross 19		Jiang 2016	242	5.11	2.3100	120	4.31	2.0300		-+	0.80	[ 0.33; 1.27]	19.7%
Ceccoll 2013 116 5.03 2.1500 110 5.05 2.1000 1 16 3.52 0.3200 152 1.121 [2.8 1.76] 2.2.8, 152 [1.28 1.76] 2.2.8,		Petramala 2014	73	6.07	2.9200	73	4.10	2.1000			1.97	[ 1.14; 2.80]	14.2%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Ceccoli 2013	116	5.03	2.1500	110	3.05	2.1000			1.98	[ 1.43; 2.53]	18.3%
Rossi 1998 1 6 5.04 0.3600 17 6 3.52 0.2200 Random effects model 671 Heterogeneity: $f^2 = 0.2576, p < 0.01$ <b>5</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b>		Rossi 2012	58	5.36	3.2200	74	8.53	28.8400			-3.17	[-9.79; 3.45]	0.5%
$ \begin{array}{c} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 $		Rossi 1998	16	5.04	0.3600	16	3.52	0.3200			1.52	[ 1.28; 1.76]	22.8%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Rossi 1995	10	5.15	2.2800	20	4.68	2.2500			0.47	[-1.25; 2.19]	o.0%
$ \frac{1}{10000000000000000000000000000000000$		Random effects model	671	70	0.04	569				<b></b>	1.29	[ 0.81; 1.78]	100.0%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	-	Heterogeneity: $I^{-} = 13\%$ , $\tau^{-}$	= 0.25	76, p <	0.01					-5 0 5			
$\frac{\operatorname{Lurgun}_{2020}}{\operatorname{Lurgun}_{2019}} \frac{156}{12} 6.5.3 \pm 2.900}{12} \frac{156}{2.7.3} (2.970) \frac{1}{2.7.7} (2.5.2)}{2.7.7} (2.5.070) \frac{1}{2.7.7} (2.5.2)}{1.7.7} (2.5.2) (2.7.7) (2.5.7) $	С	Study	Total	Mean	PA SD	Total	Mean	EH SD		Mean Difference	MD	95%-CI	Weight
$ \begin{array}{c} \mbox{Lercyan 12016} & 42 & 353 & 14100 & 153 & 273 & 0.6700 \\ \mbox{Loh 2018} & 184 & 413 & 33000 & 172 & 728 & 20900 \\ \mbox{Loh 2018} & 124 & 9413 & 13000 & 172 & 570 & 19500 \\ \mbox{Loh 2018} & 124 & 9413 & 13000 & 170 & 534 & 17300 \\ \mbox{Loc 2013} & 116 & 8.65 & 34700 & 110 & 584 & 17300 \\ \mbox{Loc 2013} & 116 & 8.65 & 34700 & 110 & 584 & 17300 \\ \mbox{Rossl 1995} & 10 & 7.37 & 2.5300 & 120 & 3.74 & 1.8600 \\ \mbox{Rossl 1995} & 10 & 7.37 & 2.5300 & 120 & 3.74 & 1.8600 \\ \mbox{Rossl 1995} & 10 & 7.37 & 2.5300 & 120 & 3.74 & 1.8600 \\ \mbox{Rossl 1995} & 10 & 7.37 & 2.5300 & 120 & 3.74 & 1.8600 \\ \mbox{Rossl 1995} & 10 & 7.37 & 2.5300 & 120 & 3.74 & 1.8600 \\ \mbox{Rossl 1995} & 10 & 7.37 & 2.5300 & 156 & 46.31 & 20.0000 \\ \mbox{Luc 2011} & 165 & 43.38 & 21.3000 & 156 & 46.31 & 20.0000 \\ \mbox{Luc 2011} & 165 & 43.38 & 21.3000 & 156 & 46.31 & 20.0000 \\ \mbox{Luc 2011} & 165 & 43.38 & 21.3000 & 156 & 46.31 & 20.0000 \\ \mbox{Luc 2011} & 165 & 43.38 & 21.3000 & 156 & 46.31 & 20.0000 \\ \mbox{Luc 2011} & 165 & 43.38 & 21.3000 & 156 & 46.31 & 20.0000 \\ \mbox{Luc 2011} & 165 & 43.38 & 21.3000 & 120 & 44.84000 \\ \mbox{Rossl 2012} & 126 & 56.8600 & 120 & 34.28 & 12.4600 \\ \mbox{Luc 2011} & 165 & 43.38 & 21.3000 & 110 & 48.44 & 48.900 \\ \mbox{Rossl 2012} & 158 & 46.38 & 21.3000 & 110 & 64.84 & 48.900 \\ \mbox{Rossl 2012} & 158 & 46.38 & 21.3000 & 116 & 27.66 & 37.4100 \\ \mbox{Ruc 2013} & 116 & 59.85 & 57.4100 & 110 & 64.84 & 48.900 \\ \mbox{Rossl 2012} & 158 & 46.38 & 21.3000 & 177 & 10.3 & 0.1900 \\ \mbox{Ruc 400} & for 108 & 22.9 & 59.1000 & 182 & 76.08 & 37.4100 \\ \mbox{Rossl 2012} & 18 & 0.81 & 0.2400 & 17 & 0.33 & 0.1700 \\ \mbox{Ruc 41} & 18 & 0.81 & 0.2400 & 17 & 0.33 & 0.1700 \\ \mbox{Ruc 41} & 18 & 0.81 & 0.2400 & 17 & 0.33 & 0.1700 \\ \mbox{Ruc 41} & 18 & 0.81 & 0.2400 & 17 & 0.33 & 0.1700 \\ \mbox{Ruc 41} & 18 & 0.81 & 0.2400 & 17 & 0.33 & 0.1700 \\ \mbox{Ruc 41} & 18 & 0.059 & 18.700 & 17 & 0.33 & 0.1700 \\ \mbox{Ruc 41} & 18 & 0.059 & 18.700 & 17 & 0.33 & 0.1700 \\ \mbox{Ruc 41} & 18 & 0.059 & 18.700 & 17 $		Tuersun 2020	156	6.13	2,9000	156	4.39	2,1300			1.74	[ 1,18: 2.30]	12.2%
Lch 2018 18 441 33000 17 278 2.0900 17 3.73 1.2500 17 2.78 2.0900 19 3.41 158, 26.205 12 158, 24.6 12.3% Cocol 2013 16 8.65 3.4700 116 5.54 1.7300 17 2.78 2.32 3.400 19 2.71 [2.00; 3.42] 11.5% Ross 2012 58 11.25 4.690 74 8.32 3.2400 19 2.231 [1.52; 4.34] 7.7% Ross 1995 16 5.00 0.540 16 3.52 0.3700 17 2.58 2.499 2.2000 14 3.52 0.3700 17 2.58 2.499 2.2000 14 3.52 0.3700 17 2.58 2.58 10 7.37 2.5300 2.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0		Lenzini 2019	42	3.53	1.4100	63	2.73	0.8700			0.80	[ 0.32; 1.28]	12.6%
Jiang 2016 $242 \ 9.11 \ 3.000 \ 120 \ 5.70 \ 1.9500 \ 5.52 \ 0.000 \ 73 \ 3.23 \ 1.2500 \ 0.000 \ 123 \ 5.51 \ 2.2500 \ 0.000 \ 123 \ 5.51 \ 2.2500 \ 0.000 \ 123 \ 5.51 \ 2.2500 \ 0.000 \ 123 \ 5.52 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.000 \ 123 \ 5.200 \ 0.0$		Loh 2018	18	4.41	3.3000	17	2.78	2.0900			1.63	[-0.19; 3.45]	6.0%
Petramala 2014 73 5.15 2.0900 73 3.23 1.2500 Ceccoll 2013 116 865 34700 116 5.94 1.730 115 5.94 1.930 115 5.94 1.930 114 1.944 1.940 114 1.940 114 1.940 114 1.940 114 1.940 114 1.940 114 1.940 114 1.940 114 1.940 114 1.940 114 1.940 114 1.940 114 1.940 117 1.030 1.900 114 1.940 117 1.030 1.900 114 1.940 117 1.030 1.900 114 1.94		Jiang 2016	242	9.11	3.8000	120	5.70	1.9500			3.41	[ 2.82; 4.00]	12.1%
Ceccol 2013 116 8.65 34700 110 5.54 17300 Pilz 2012 10 7.14 22800 182 4.89 2200 Rossi 1095 10 7.37 25300 20 3.74 1.8800 Random effects model 741 831 Heterogeneity: $h^2 = 665$ , $t^2 = 0.6602$ , $p = 0.01$ <b>D</b> <b>Study Total Mean PA</b> <b>T</b> <b>Study Total Mean PA</b> <b>T</b> <b>Study Total Mean PA</b> <b>T</b> <b>Study Total Mean PA</b> <b>T</b> <b>Study Total Mean SD</b> <b>T</b> <b>Study Total Mean SD</b> <b>Total Mean SD</b> <b>Total Mean SD</b> <b>Mean Difference MD 95%-CI Weight</b> <b>Study Total Mean SD</b> <b>Total Mean SD</b> <b>Total Mean SD</b> <b>Total Mean SD</b> <b>Total Mean SD</b> <b>Mean Difference MD 95%-CI Weight</b> <b>Study Total Mean SD</b> <b>Total Mean SD</b> <b>Mean Difference MD 95%-CI Weight</b> <b>Study Total Mean SD</b> <b>Total Mean SD</b> <b>Mean Difference MD 95%-CI Weight</b> <b>Section = LS</b> <b>Loh</b> 2018 <b>118</b> 1.06 0.1400 177 1.03 0.1900 <b>4.0</b> <b>5.0</b> (-0.05 0 0.050 01 0.15 1.15.85 3.1700 <b>5.0</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.8</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b> <b>5.9</b>		Petramala 2014	73	5.15	2.0900	73	3.23	1.2500			1.92	[ 1.36; 2.48]	12.3%
Ross 2012       58       1125       4489       2000       235       1254       439       2000       235       1254       439       2000       235       1254       439       2000       14       145       145       132%       61%       132%       61%       132%       61%       144       145       1125       157       77%       157       15		Ceccoli 2013	116	8.65	3.4700	110	5.94	1.7300		÷	2.71	[ 2.00; 3.42]	11.5%
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		Rossi 2012	58	11.25	4.6900	74	8.32	3.2400			2.93	[1.52; 4.34]	7.7%
$ \begin{array}{c} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 $		Pliz 2012 Rossi 1998	10	5.00	2.8300	182	4.89	0.3700		100	2.25	[ 0.47; 4.03]	6.1% 13.2%
Random effects model 741 Heterogeneity: $t^2 = 86\%, t^2 = 0.06002, p < 0.01$ <b>2</b> .16 [1.57; 2.75] 100.0% <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b>		Rossi 1995	10	7.37	2.5300	20	3.74	1.6800			- 3.63	[ 1.90; 5.36]	6.3%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Random effects model Heterogeneity: $I^2 = 86\%$	741	602. p <	0.01	831			_		2.16	[ 1.57; 2.75]	100.0%
Study Total Mean $\stackrel{\text{SD}}{\text{SD}}$ Total Mean $\stackrel{\text{SD}}{\text{SD}}$ $\stackrel{\text{Mean}}{\text{SD}}$ $\stackrel{\text{MD}}{\text{SD}}$ $\stackrel{\text{SD}}{\text{SD}}$ $\stackrel{\text{SD}}{\text{SD}}$ $\stackrel{\text{MD}}{\text{SD}}$ $\stackrel{\text{SD}}{\text{SD}}$ $\stackrel{\text{SD}$	D		0.00	002, p	DA			EU	-4	-2 0 2 4			
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Study	Total I	Mean	SD	Total I	Mean	SD		Mean Difference	MD	95% <b>-</b> C	I Weight
Loh 2018 18 22.34 7.3700 17 20.54 15.8000 182 12.1600 10 43.42 812.1600 10 43.42 812.1600 10 43.42 812.1600 10 63.83 0.000 10 4.29 12.157.8 5.61 14.7% 222.000 110 64.84 44.8900 20.65 12.0 58 46.53 26.1700 74 47.02 22.000 10 73 82.20 439 3000 10 4.29 15.79; 5.61 14.7% 2.23 (5.68 37.4100 10 62.29 59.1000 182 76.06 37.4100 17 1.03 0.1900 10 62.29 59.1000 17 1.03 0.1900 10 62.29 59.1000 17 1.03 0.1900 10 60.51 0.05 [0.012] 18.4% -0.10 [0.16; 0.04] 32.4% -0.10 [0.16; 0.04] 32.4% -0.10 [0.16; 0.04] 32.4% -0.05 [0.017; 0.08] 50.8% Heterogeneity: $l^2 = 76\%$ , $r^2 = 0.0024$ 50 00 73 0.84 0.1200 50 0.05 0.1 0.15 50 0.05 0.1 0.15 50 0.05 0.1 0.15 50 0.05 0.1 0.15 50 0.05 0.1 0.15 50 0.05 0.1 0.15 50 0.05 0.1 0.15 50 0.05 0.1 0.15 50 0.05 0.1 0.15 50 0.05 0.1 0.15 50 0.05 0.1 0.15 50 0.05 0.05		Tuersun 2020	156 4	48.38 2	1.3200	156	46.31	20.0000		: <del>E</del>	2.07	[-2.52; 6.66	6] 16.8%
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		Loh 2018	18 2	22.34	7.3700	17 :	20.54	15.8000			1.80	[-6.45; 10.05	] 15.7%
$ \begin{array}{c} \text{Pertamata} 2014 & 13 & 41.39 & 31.170 & 16 & 68.43 & 43.99 & 39.900 \\ \text{Ceccoil 2013} & 116 & 59.8 & 57.4100 & 116 & 68.48 & 44.89 & 59.757 & 5.81 & 14.7\% \\ \text{Rossi 2012} & 58 & 46.63 & 26.1700 & 182 & 76.06 & 37.4100 \\ \text{Pitz 2012} & 10 & 82.29 & 59.1000 & 182 & 76.06 & 37.4100 \\ \text{Heterogenelty: } l^2 = 86\%, r^2 = 172.3573, p < 0.01 \\ \text{Heterogenelty: } l^2 = 86\%, r^2 = 172.3573, p < 0.01 \\ \text{F} \\ \begin{array}{c} \text{Section = LS} \\ \text{Loh 2018} & 18 & 1.06 & 0.1400 & 17 & 1.03 & 0.1900 \\ \text{Petramata 2014} & 73 & 1.01 & 0.1700 & 73 & 1.11 & 0.1700 \\ \text{Petramata 2014} & 73 & 1.01 & 0.1700 & 73 & 1.11 & 0.1700 \\ \text{Random effects model } 91 \\ \text{Petramata 2014} & 73 & 0.84 & 0.1600 & 73 & 0.84 & 0.1200 \\ \text{Random effects model } 91 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 66\%, r^2 = 0.024, p = 0.03 \\ \text{Heterogeneity: } l^2 = 8\%, r^2 = 2164.9000, p < 0.01 \\ \text{Heterogeneity: } l^2 = 8\%, r^2 = 2164.9000, p < 0.01 \\ \text{Heterogeneity: } l^2 = 8\%, r^2 = 2164.9000, p < 0.01 \\ \text{Heterogeneity: } l^2 = 8\%, r^2 = 2164.9000, p < 0.01 \\ \text{Heterogeneity: } l^2 = 8\%, r^2 = 2164.9000, p < 0.01 \\ \text{Heterogeneity: } l^2 = 8\%, r^2 = 2164.9000, p < 0$		Jiang 2016	242 2	29.10 1	4.5400	120 3	34.28	12.1600			-5.18	[-8.02; -2.34	] 17.1%
$ \begin{array}{c} \begin{array}{c} \begin{array}{c} 0 \text{ dots} 12015 & 116 & 32.03 & 0.7410 \\ \text{Ross} 12012 & 10 & 82.29 & 59.1000 & 182 & 76.06 & 37.4100 \\ \text{Pliz 2012 } & 10 & 82.29 & 59.1000 & 182 & 76.06 & 37.4100 \\ \text{Heterogeneity; } l^2 = 86\%, \tau^2 = 172.3573, p < 0.01 \end{array} \\ \begin{array}{c} \begin{array}{c} \text{F} \\ \begin{array}{c} \text{Sudy} \\ \text{Total Mean} \\ \text{Section = LS} \\ \text{Loh 2018 } 18 & 1.06 & 0.1400 & 17 & 1.03 & 0.1900 \\ \text{Petramala 2014 } 73 & 1.01 & 0.1700 & 73 & 1.11 & 0.1700 \\ \text{Petramala 2014 } 73 & 0.84 & 0.620 & 17 & 0.83 & 0.1700 \\ \text{Heterogeneity; } l^2 = 76\%, \tau^2 = 0.0024, p = 0.04 \\ \end{array} \\ \begin{array}{c} \text{Section = FN} \\ \text{Loh 2018 } 18 & 0.81 & 0.2400 & 17 & 0.83 & 0.1700 \\ \text{Heterogeneity; } l^2 = 0.054, \tau^2 = 0.0024, p = 0.04 \\ \end{array} \\ \begin{array}{c} \text{F} \\ \text{Sudy} \\ \text{Total Mean} \\ \end{array} \\ \begin{array}{c} \text{Soluto 0.140 } 182 \\ \text{Heterogeneity; } l^2 = 0.056, \tau^2 = 0.0024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 0.056, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 0.056, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 0.056, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 0.056, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 0.056, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 96\%, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 95\%, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 95\%, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 95\%, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 95\%, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 95\%, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 95\%, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 95\%, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 95\%, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 95\%, \tau^2 = 0.024, p = 0.03 \\ \text{Heterogeneity; } l^2 = 95\%, \tau^2 = 0.025\%, p = 0.03 \\ \text{Heterogeneity; } l^2 = 85\%, \tau^2 = 2.025\%, p = 0.03 \\ \text{Heterogeneity; } l^2 = 85\%, \tau^2 = 2.025\%, p = 0.03 \\ \text{Heterogeneity; } l^2 = 85\%, \tau^2 = 2.025\%, p < 0.01 \\ \end{array}$		Ceccoli 2013	116	44.39 3 50.85 3	7 4100	110	64.84 J	39.9000 ·			-37.05	-49.20; -20.04 [-15.70: 5.81	1 14.4%
Pliz 2012 10 0 22.29 59.1000 192 76.06 37.4100 Pliz 2012 10 0 22.29 59.1000 192 76.06 37.4100 Heterogeneity: $l^2 = 86\%$ , $r^2 = 172.3573$ , $p < 0.01$ Total Mean $PA$ Sudy Total Mean $PA$ Section = LS Loh 2018 18 1.06 0.1400 17 1.03 0.1900 Petramala 2014 73 1.01 0.1700 73 1.11 0.1700 Random effects model 91 Heterogeneity: $l^2 = 76\%$ , $r^2 = 0.04$ Section = FN Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Petramala 2014 73 0.84 0.1600 73 0.84 0.1200 Heterogeneity: $l^2 = 0\%$ , $r^2 = 0.024$ , $p = 0.04$ F Sudy Total Mean $PA$ Random effects model 91 Petramala 2014 73 0.84 0.1600 73 0.84 0.1200 Heterogeneity: $l^2 = 0\%$ , $r^2 = 0.079$ Random effects model 91 Petramala 2014 73 1.63.30 33.9000 73 0.73 0.74 0.46.7000 Heterogeneity: $l^2 = 0\%$ , $r^2 = 0.079$ Random effects model 91 Petramala 2014 73 1.05 9 18.7000 17 61.29 26.2700 Petramala 2014 18 70.59 18.7000 17 61.29 26.2700 Petramala 2014 18 70.59 18.7000 17 61.29 26.2700 Petramala 2014 73 163.30 33.9000 73 87.40 46.7000 Petramala 2014 73 163.30 33.9000 73 87.40 46.7000 Petramala 2014 73 163.03 73.9000 17 61.29 26.2700 Petramala 2014 73 163.03 33.9000 73 87.40 46.7000 Petramala 2014 73 163.03 73.9000 17 61.29 26.2700 Petramala 2014 73 163.03 73.9000 17 61.29 26.2700 Petramala 2014 73 163.03 73.9000 17 61.29 26.2700 Petramala 2014 73 163.03 73.9000 73 87.40 46.7000 Petramala 2014 73 163.20 75.90 [52.66; 89.14] 50.2% Petramala 2014 73 163.9000, $p < 0.01$		Rossi 2012	58	46.63.2	6 1700	74	47 20	22 0000			-0.57	[-8.97: 7.83	15.7%
Random effects model 673 Heterogeneity: $l^2 = 86\%, t^2 = 172.3573, p < 0.01$ Total Mean $Pa$ Total Mean $Bb$ Mean Difference MD 95%-Cl Weight Section = LS Loh 2018 18 1.06 0.1400 17 1.03 0.1900 Petramala 2014 73 1.01 0.1700 73 1.11 0.1700 Random effects model 91 Heterogeneity: $l^2 = 76\%, t^2 = 0.0062, p = 0.04$ Section = FN Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Heterogeneity: $l^2 = 76\%, t^2 = 0.0062, p = 0.04$ Section = FN Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Heterogeneity: $l^2 = 0\%, t^2 = 0.04$ Section = FN Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Heterogeneity: $l^2 = 0\%, t^2 = 0.04$ Section = FN Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Heterogeneity: $l^2 = 0\%, t^2 = 0.04$ Section = FN Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Heterogeneity: $l^2 = 0\%, t^2 = 0.079$ Random effects model 91 Heterogeneity: $l^2 = 0\%, t^2 = 0.079$ Random effects model 91 Heterogeneity: $l^2 = 0\%, t^2 = 0.079$ Random effects model 91 Heterogeneity: $l^2 = 0\%, t^2 = 0.079$ Random effects model 91 Heterogeneity: $l^2 = 0\%, t^2 = 0.079$ Random effects model 91 0.03 (-0.05; 0.06] 35.1% -0.05 (-0.05; 0.06] 35.1% -0.05 (-0.05; 0.06] 35.1% -0.05 (-0.05; 0.06] 35.1% -0.00 (-0.05; 0.04] 49.2% -0.05 (-0.05; 0.04] 49.2% -0.05 (-0.05; 0.06] 35.1% -0.00 (-0.05; 0.04] 49.2% -0.05 (-0.05; 0.06] 35.1% -0.00 (-0.05; 0.04] 49.2% -0.05 (-0.05; 0.06] 35.1% -0.05 (-0.05; 0.05] 30.1% -0.05 (-0.05; 0.06] 30.1%		Pliz 2012	10	82.29 5	9.1000	182	76.06	37.4100	_	<b>#</b>	6.23	[-30.80; 43.26	5.6%
Random effects model b73 $732$ Heterogeneity: $l^2 = 86\%, \tau^2 = 172.3573, p < 0.01$ <b>E</b> <b>Study</b> <b>Total Mean</b> <b>SD</b> <b>Total Mean</b> <b>SD</b> <b>Total Mean</b> <b>SD</b> <b>Total Mean</b> <b>SD</b> <b>Mean Difference</b> <b>MD</b> <b>95%-CI Weight</b> <b>Section = LS</b> Loh 2018 <b>18</b> 1.06 0.1400 17 1.03 0.1900 Petramala 2014 73 1.01 0.1700 73 1.11 0.1700 Random effects model 91 90 Heterogeneity: $l^2 = 76\%, \tau^2 = 0.0062, p = 0.04$ <b>Section = FN</b> Loh 2018 <b>18</b> 0.81 0.2400 17 0.83 0.1700 <b>Petramala 2014</b> 73 0.84 0.1600 73 0.84 0.1200 <b>Petramala 2014</b> 18 0.81 0.2400 17 0.83 0.1700 <b>Petramala 2014</b> 18 0.799 18.7000 17 61.29 26.2700 <b>Petramala 2014</b> 18 70.59 18.7000 17 61.29 26.2700 <b>Petramala 2014</b> 73 163.30 33.39000 73 87.40 46.7000 <b>Petramala 2014</b> 73 163.30 33.9000 73 87.40 46.7000 <b>Petramala 2014</b> 73 163.30 3.9000 73 87.40 46.7000 <b>Petramala 2014</b> 10 81.5000 17 61.29 26.2700 <b>Petramala 2014 Petramala 2014 Petrama</b>													-
		Random effects model Heterogeneity: $J^2 = 86\% \tau^2$	673 = 172 3	8573 n ·	< 0.01	732			Г <b>—</b> —		-6.15	[-16.85; 4.56	] 100.0%
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	-	neterogeneny. r = 0070, r	- 172.0	, or 0, p	- 0.01				-40	-20 0 20 40			
Section = LS Loh 2018 18 1.06 0.1400 17 1.03 0.1900 Petramala 2014 73 1.01 0.1700 73 1.11 0.1700 Random effects model 91 Heterogeneity: $l^2 = 76\%$ , $r^2 = 0.0082$ , $p = 0.04$ Section = FN Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Petramala 2014 73 0.84 0.1800 73 0.84 0.1200 Heterogeneity: $l^2 = 0.0024$ , $p = 0.03$ Test for subgroup differences: $r_1^2 = 0.42$ , df = 1 ( $p = 0.52$ ) F Study Total Mean PA A Petramala 2014 73 163.30 33.9000 17 61.29 26.2700 Petramala 2014 73 163.30 33.9000 73 87.40 46.7000 Random effects model 91 Heterogeneity: $l^2 = 98\%$ , $r^2 = 2164.9600$ , $p < 0.01$	E	Study	Total	Mean	PA SD	Total	Mean	EH SD		Mean Difference	MD	95%-CI	Weight
Loh 2018 18 1.06 0.1400 17 1.03 0.1900 Petramala 2014 73 1.01 0.1700 73 1.11 0.1700 Random effects model 91 Heterogeneity: $l^2 = 76\%$ , $\tau^2 = 0.0062$ , $p = 0.04$ Section = FN Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Petramala 2014 73 0.84 0.1600 73 0.84 0.1200 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0.024$ , $p = 0.03$ Test for subgroup differences: $\chi_1^2 = 0.42$ , df = 1 ( $p = 0.52$ ) F Study Total Mean SD Total Mean Effects model 91 Loh 2018 18 70.59 18.7000 17 61.29 26.2700 Petramala 2014 73 163.30 33.9000 73 87.40 46.7000 Random effects model 91 0.03 [-0.08; 0.14] 18.4% -0.05 [-0.17; 0.08] 50.8% -0.02 [-0.16; 0.12] 14.1% -0.00 [-0.05; 0.04] 49.2% -0.03 [-0.09; 0.03] 100.0% Heterogeneity: $l^2 = 98\%$ , $\tau^2 = 2.164.9600$ , $p < 0.01$		Section = LS								÷			
Petramala 2014 73 1.01 0.1700 73 1.11 0.1700 Random effects model 91 90 Heterogeneity: $l^2 = 76\%$ , $\tau^2 = 0.0052$ , $p = 0.04$ Section = FN Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Petramala 2014 73 0.84 0.1600 73 0.84 0.1200 Petramala 2014 73 0.84 0.1600 73 0.84 0.1200 Random effects model 91 90 Heterogeneity: $l^2 = 66\%$ , $\tau^2 = 0.0024$ , $p = 0.03$ Test for subgroup differences: $\chi_1^2 = 0.42$ , df = 1 ( $p = 0.52$ ) F Study Total Mean SD Total Mean EH Loh 2018 18 70.59 18.7000 17 61.29 26.2700 Petramala 2014 73 163.30 3.8000 73 87.40 46.7000 Random effects model 91 90 Heterogeneity: $l^2 = 98\%$ , $\tau^2 = 2164.9600$ , $p < 0.01$		1 -1-0040	18	1.06	0.1400	17	1.03	0.1900			0.03	[-0.08; 0.14]	18.4%
Kandom effects model       91       90         Heterogeneity: $l^2 = 76\%$ , $\tau^2 = 0.0062$ , $p = 0.04$ Section = FN         Loh 2018       18       0.81       0.2400       17       0.83       0.1700         Petramala 2014       73       0.84       0.1800       73       0.84       0.1200         Random effects model       91       90       90       90       90       -0.05 [-0.17; 0.08]       50.3%         Random effects model       91       90       90       90       -0.03 [-0.05; 0.04]       49.2%         Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.03$ 180       -0.15-0.1-0.05 0       0.05 0.1 0.15       -0.03 [-0.09; 0.03] 100.0%         Heterogeneity: $l^2 = 66\%$ , $\tau^2 = 0.0024$ , $p = 0.03$ -0.15-0.1-0.05 0       0.05 0.1 0.15       -0.15-0.1-0.05 0       0.05 0.1 0.15         F       Study       Total Mean       SD       Mean Difference       MD       95%-CI Weight         Loh 2018       18       70.59 18.7000       17       61.29 26.2700       -9.30       [-5.88; 24.48] 49.8%         Petramala 2014       73 163.30 33.9000       73 87.40 46.7000       -5.50       0       50       100.52         Heterogeneity: $l^2 = 98\%$ , $\tau^2 = 2164.9600$ , $p < 0.01$		Lon 2018	10						_			1046.0041	22 40/
Section = FN Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Petramala 2014 73 0.84 0.1600 73 0.84 0.1200 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0.024$ , $p = 0.03$ Test for subgroup differences: $\chi_1^2 = 0.42$ , df = 1 ( $p = 0.52$ ) F Study Total Mean SD Total Mean SD Total Mean SD Total Mean Difference MD 95%-CI Weight Loh 2018 18 70.59 18.7000 17 61.29 26.2700 Petramala 2014 73 163.30 33.9000 73 87.40 46.7000 Random effects model 91 90 Heterogeneity: $l^2 = 98\%$ , $\tau^2 = 2164.9600$ , $p < 0.01$		Petramala 2014	73	1.01	0.1700	73	1.11	0.1700		•	-0.10	[-0.16; -0.04]	32.4%
Loh 2018 18 0.81 0.2400 17 0.83 0.1700 Petramala 2014 73 0.84 0.1600 73 0.84 0.1200 Random effects model 91 90 Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0.024$ , $p = 0.03$ Test for subgroup differences: $\chi_1^2 = 0.42$ , df = 1 ( $p = 0.52$ ) F PA EH Study Total Mean SD Total Mean SD Total Mean SD Total Mean PA EH Loh 2018 18 70.59 18.7000 17 61.29 26.2700 Petramala 2014 73 163.30 33.9000 73 87.40 46.7000 Random effects model 91 90 Heterogeneity: $l^2 = 98\%$ , $\tau^2 = 2164.9600$ , $p < 0.01$		Petramala 2014 Random effects model Heterogeneity: / <sup>2</sup> = 76%, n	73   91   <sup>2</sup> = 0.00	1.01 062, p =	0.1700 0.04	73 90	1.11	0.1700			-0.10 -0.05	[-0.17; 0.08]	50.8%
Pertamana 2014       73       0.84       0.1000       73       0.84       0.1200         Random effects model       91       90       90       -0.00 [-0.05; 0.05]       35.1%         Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0$ , $p = 0.79$ -0.00 [-0.05; 0.04]       49.2%         Random effects model       182       180         Heterogeneity: $l^2 = 66\%$ , $\tau^2 = 0.024$ , $p = 0.03$ -0.15-0.1-0.05       0       0.03 [-0.09; 0.03]       100.0%         F       PA       EH       SD       tel Mean       SD       Mean Difference       MD       95%-CI Weight         Loh 2018       18       70.59       18.7000       17       61.29       26.2700       -75.90       [62.66; 89.14]       50.2%         Random effects model       91       90       -100       -50       0       50       100		Petramala 2014 Random effects model Heterogeneity: / <sup>2</sup> = 76%, 1 Section = FN	73   91 ; <sup>2</sup> = 0.00	1.01 062, p =	0.1700 0.04	73 90	1.11	0.1700			-0.10 -0.05	[-0.17; 0.08]	50.8%
Notice of the construction of the construle of the construction of the constructio		Petramala 2014 Random effects model Heterogeneity: / <sup>2</sup> = 76%, n Section = FN Loh 2018	73 1 91 2 = 0.01	1.01 062, <i>p</i> = 0.81	0.1700 0.04 0.2400	73 90 17	0.83	0.1700			-0.10 -0.05	[-0.16; -0.04] [-0.17; 0.08]	32.4% 50.8%
$ \begin{array}{c} \text{-100} \text{ Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\ \text{Heterogeneity: } l^2 = 98\%, \tau^2 = 2164.9600, p < 0.01 \\$		Petramala 2014 Random effects model Heterogeneity: / <sup>2</sup> = 76%, n Section = FN Loh 2018 Petramala 2014 Random effects model Heterogeneity: / <sup>2</sup> = 0%, - <sup>2</sup>	73   91 ; <sup>2</sup> = 0.0  18 73   91 = 0.0	1.01 062, <i>p</i> = 0.81 0.84 = 0.79	0.1700 0.04 0.2400 0.1600	73 90 17 73 90	1.11 0.83 0.84	0.1700 0.1700 0.1200			-0.10 -0.05 -0.02 0.00 -0.00	[-0.16; -0.04] [-0.17; 0.08] [-0.16; 0.12] [-0.05; 0.05] [-0.05; 0.04]	32.4% 50.8% 14.1% 35.1% 49.2%
$ \begin{array}{c} \text{F} \\ \text{Study} \\ \text{Total Mean} \\ \text{Study} \\ \text{Total Mean} \\ \text{SD Total Mean} \\ \text$		Petramala 2014 Random effects model Heterogeneity: <i>I</i> <sup>2</sup> = 76%, n Section = FN Loh 2018 Petramala 2014 Random effects model Heterogeneity: <i>I</i> <sup>2</sup> = 0%, <i>r</i> <sup>2</sup>	73 I 91 : <sup>2</sup> = 0.01 I 8 73 I 91 = 0, p :	1.01 062, <i>p</i> = 0.81 0.84 = 0.79	0.1700 0.04 0.2400 0.1600	73 90 17 73 90	1.11 0.83 0.84	0.1700 0.1700 0.1200	_		-0.10 -0.05 -0.02 0.00 -0.00	[-0.16; -0.04] [-0.17; 0.08] [-0.16; 0.12] [-0.05; 0.05] [-0.05; 0.04]	32.4% 50.8% 14.1% 35.1% 49.2%
Study         Total Mean         SD         Total Mean         SD         Mean Difference         MD         95%-Cl Weight           Loh 2018         18         70.59         18.7000         17         61.29         26.2700         9.30         [-5.88; 24.48]         49.8%           Petramala 2014         73         163.30         33.9000         73         87.40         46.7000         75.90         [62.66; 89.14]         50.2%           Random effects model         91         90         -100         -50         0         50         100		Lon 2018 Petramala 2014 Random effects model Heterogeneity: $l^2 = 76\%$ , 1 Section = FN Loh 2018 Petramala 2014 Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2$ <b>Random effects model</b> Heterogeneity: $l^2 = 6\%$ , 1 Text for subscript of the subsc	73 91 $c^2 = 0.01$ 18 73 191 = 0, p 182 2 = 0.00	1.01 062, <i>p</i> = 0.81 0.84 = 0.79	0.1700 0.04 0.2400 0.1600 0.1600	73 90 17 73 90 <b>180</b>	1.11 0.83 0.84	0.1700 0.1700 0.1200			-0.10 -0.05 -0.02 0.00 -0.00 -0.03	[-0.16; -0.04] [-0.17; 0.08] [-0.05; 0.05] [-0.05; 0.05] [-0.09; 0.03]	14.1% 35.1% 49.2%
Loh 2018       18       70.59       18.7000       17       61.29       26.2700       9.30       [-5.88; 24.48]       49.8%         Petramala 2014       73       163.30       33.9000       73       87.40       46.7000       9.30       [-5.88; 24.48]       49.8%         Random effects model       91       90       42.71       [-22.56; 107.97]       100.0%         Heterogeneity: $l^2$ = 98%, $\tau^2$ = 2164.9600, $p < 0.01$ 90       90	F	Detramala 2014 Random effects mode Heterogeneity: $l^2 = 76\%$ , 1 Section = FN Loh 2018 Petramala 2014 Random effects mode Heterogeneity: $l^2 = 0\%$ , $t^2$ <b>Random effects mode</b> Heterogeneity: $l^2 = 66\%$ , 1 Test for subgroup differen	73 $1$	<ul> <li>1.01</li> <li>0.62, p =</li> <li>0.81</li> <li>0.84</li> <li>0.79</li> <li>0.24, p =</li> <li>0.42,</li> </ul>	0.1700 0.2400 0.2400 0.1600 = 0.03 df = 1 (p	73 90 17 73 90 180 = 0.52)	1.11 0.83 0.84	0.1700 0.1700 0.1200	-0.15-0	.1-0.05 0 0.05 0.1 0.	-0.10 -0.05 -0.02 0.00 -0.00 -0.00	[-0.16; 0.124] [-0.17; 0.08] [-0.05; 0.05] [-0.05; 0.04] [-0.09; 0.03]	14.1% 35.1% 49.2%
Random effects model         91         90           Heterogeneity: /² = 98%, τ² = 2164.9600, p < 0.01	F	Lon 2018 Petramala 2014 Random effects model Heterogeneity: $l^2 = 76\%$ , $r$ Section = FN Loh 2018 Petramala 2014 Random effects model Heterogeneity: $l^2 = 0\%$ , $r^2$ <b>Random effects model</b> Heterogeneity: $l^2 = 66\%$ , $r$ Test for subgroup differen	73 1   91 $t^2 = 0.00$ 188 73 1   91 = 0, p 1   182 $t^2 = 0.00$ $ces: \chi_1^2$ Total	$\begin{array}{c} 1.01\\ 062, p = \\ 0.81\\ 0.84\\ = 0.79\\ 024, p = \\ 0.42, \\ \end{array}$	0.1700 0.2400 0.2400 0.1600 c 0.03 df = 1 (p P/ SI	73 90 17 73 90 180 = 0.52) 2 7 7 7 7 3 90	1.11 0.83 0.84	0.1700 0.1700 0.1200 0.1200	-0.15-0	0.1-0.05 0 0.05 0.1 0.1 Mean Difference	-0.10 -0.05 -0.02 0.00 -0.00 -0.00 15 MD	[-0.16; 0.12] [-0.05; 0.05] [-0.09; 0.03]	52.4% 50.8% 14.1% 35.1% 49.2% 100.0%
Heterogeneity: $l^2 = 98\%$ , $\tau^2 = 2164.9600$ , $p < 0.01$ -100 -50 0 50 100	F	Lon 2018 Petramala 2014 Random effects mode Heterogeneity: /² = 76%, 1 Section = FN Loh 2018 Petramala 2014 Random effects mode Heterogeneity: /² = 66%, 1 Test for subgroup differen Study Loh 2018 Petramala 2014	73 191 $r^2 = 0.0$ 18 73 191 = 0, p $r^2 = 0.00$ $r^2 = 0.00$ r	= 0.81 $= 0.79$ $= 0.42, p = = 0.42, p = = 0.42, mean$ $= 0.42, mean$ $= 0.59$	0.1700 0.2400 0.1600 0.1600 0.1600 0.1600 18.7001 33.9001	73 90 17 73 90 180 = 0.52) 0 <b>7</b> 73 0 17 0 73	1.11 0.83 0.84 1 <b>Mear</b> 7 61.29 3 87.40	0.1700 0.1700 0.1200 EF 50 26.2700 0 46.7000	-0.15-0	0.1-0.05 0 0.05 0.1 0.1 Mean Difference	-0.10 -0.02 0.00 -0.00 15 <b>MD</b> 9.30 75.90	[-0.16; 0.12] [-0.16; 0.12] [-0.05; 0.05] [-0.05; 0.04] [-0.09; 0.03] 95% [-5.88; 24. [62.66; 89]	52.4% 50.8% 14.1% 35.1% 49.2% 100.0% -CI Weight 48] 49.8% 14] 50.2%
-100 -50 0 50 100	F	Lon 2018 Petramala 2014 Random effects model Heterogeneity: / <sup>2</sup> = 76%, 1 Section = FN Loh 2018 Petramala 2014 Random effects model Heterogeneity: / <sup>2</sup> = 66%, 1 Test for subgroup differen Study Loh 2018 Petramala 2014 Random effects model	73 1   91 $t^2 = 0.0$ 18 73 1   91 = 0, p 1   92 1   92 1   91 = 0, p 1   92 1   92 1	<ul> <li>1.01</li> <li>062, p =</li> <li>0.81</li> <li>0.84</li> <li>0.79</li> <li>024, p =</li> <li>0.42,</li> <li>Mean</li> <li>70.59</li> <li>163.30</li> </ul>	0.1700 0.2400 0.1600 0.1600 df = 1 (p P/ SI 18.7000 33.9000	$73 \\ 90 \\ 17 \\ 73 \\ 90 \\ 180 \\ = 0.52) \\ 0 \\ Tota \\ 0 \\ 17 \\ 0 \\ 73 \\ 0 \\ a \\ a$	0.83 0.84 0.84 1 Mear 7 61.29 3 87.40	0.1700 0.1700 0.1200 EF SE 9 26.2700 0 46.7000	-0.15-0	0.1-0.05 0 0.05 0.1 0.1 Mean Difference	-0.10 -0.02 0.00 -0.00 15 MD 9.30 75.90 - 42.71	[-0.16; 0.12] [-0.16; 0.12] [-0.05; 0.05] [-0.05; 0.04] [-0.09; 0.03] [-5.88; 24, [ 62.66; 89] [-22.56: 107]	52.4% 50.8% 14.1% 35.1% 49.2% 100.0% -CI Weight 48] 49.8% 14] 50.2%
	F	Lon 2018 Petramala 2014 Random effects model Heterogeneity: / <sup>2</sup> = 76%, 1 Section = FN Loh 2018 Petramala 2014 Random effects model Heterogeneity: / <sup>2</sup> = 66%, 1 Test for subgroup differen Study Loh 2018 Petramala 2014 Random effects model Heterogeneity: / <sup>2</sup> = 98%, t	73 1 = 91 $2^{2} = 0.0$ 18 73 1 = 91 = 0, p 1 = 182 $r^{2} = 0.00$ ces: $\chi^{2}_{1}$ Total 18 73 91 2 73 73 73 1 = 0.00 73 1 = 0.00 2 1 = 0.00 2 1 = 0.00 2 1 = 0.00 2 2 = 0.00 2 2 = 0.00 2 2 = 0.00 2 =	<ul> <li>1.01</li> <li>0.62, p =</li> <li>0.81</li> <li>0.84</li> <li>0.79</li> <li>0.24, p =</li> <li>0.42,</li> <li>Mean</li> <li>70.59</li> <li>163.30</li> <li>4.9600, j</li> </ul>	0.1700 0.2400 0.2400 0.1600 = 0.03 df = 1 (p P/ St 18.700 33.9000 p < 0.01	73 90 17 73 90 180 = 0.52) 0 Tota 0 17 0 73 90	1.11 0.83 0.84 ) ) I Mear 7 61.29 3 87.40	0.1700 0.1700 0.1200 EF SE 9 26.2700 0 46.7000	-0.15-0	0.1-0.05 0 0.05 0.1 0.1 Mean Difference	-0.10 -0.02 0.00 -0.00 -0.00 15 MD 9.30 75.90 - 42.71	[-0.16; 0.12] [-0.16; 0.12] [-0.05; 0.05] [-0.05; 0.04] [-0.09; 0.03] [-0.09; 0.03] [-5.88; 24 [ 62.66; 89 [-22.56; 107.	52.4% 50.8% 14.1% 35.1% 49.2% 100.0% -CI Weight 48] 49.8% 14] 50.2%

	Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD	95%	-ci w	leiaht
	0					0.00		-	0.00			
	Gravvanis 2021 Asbach 2020	63	2.35	0.1100	63	2.38 0	0.1100		-0.03	[-0.07; 0.0 [-0.12; -0.4	∪1j 1 ⊓⊿1 4	15.4%
	Adolf 2020	36	2.33	0.0800	60 36	2.50 0	).1500		-0.08	[-0.12; -0.0 [-0.12: 0.0	041 1 001 1	+.0%
	Loh 2018	15	2.26	0.0300	15	2.30 0	0.0800	-	-0.04	[-0.08; 0.0	00] 1	4.4%
	Jiang 2016	99	2.16	0.1000	99	2.30 0	0.1300		-0.14	[-0.17; -0.1	11] 1	16.7%
	Geccoli 2013 Salcuni 2012	40	4.45	0.2500	40 0	4.55 0	).2500 ).6100 -	-	-0.10	[-0.21; 0.0 [-0.63: 0.4	∪1] 43]	5.4% 0.3%
	Rossi 2012	9 46	2.30	0.1000	46	2.32 0	).1100 -	-	-0.08	[-0.12; -0.0	04] 1	4.5%
	Pliz 2012	10	2.26	0.1000	10	2.35 0	.1200		-0.09	[-0.19; 0.0	01]	6.5%
	Random effects model Heterogeneity: $J^2 = 66\%$ , $\tau^2$	<b>378</b> = 0.00	)11. p <	0.01	378		r	÷	-0.08 [	-0.11; -0.0	05] 10	00.0%
R							-0	.6 -0.4 -0.2 0 0.2 0.4 0	.6			
0	Study	⊺ota	l Mear	before 1 SD	Total	Mean	after SD	Mean Difference	MD	95%-	CI We	eight
	Gravvanis 2021	63	5.75	5 8.1600	63	4.40	6.2600		1.35	[-1.19; 3.8	9] (	6.2%
	Adolf 2020 liang 2016	36	5 4.96 5 1 1	5 2.3200 3 2 7600	36	2.87	1.8500		2.09	[1.12; 3.0 [1.96:3.1	6] 18 81 21	8.3% 2.9%
	Ceccoli 2013	40	5.10	2.1800	40	4.80	2.2500		0.30	[-0.67; 1.2	7] 1	8.3%
	Salcuni 2012	9	6.78	3 4.9000	9	4.49	3.5900		- 2.29	[-1.68; 6.2	6]	3.0%
	Rossi 2012 Maniero 2012	46	5.66	5 3.4000 1 2000	46	4.11	2.3000		1.55	0.36; 2.7	4] 1	5.7% 5.5%
	Random effects model	31 324	, 7.00	J 1.2000	31 324	5.10	3.2000		1.72 [	[ <b>1.00; 2.4</b>	4] 10	0.0%
~	Heterogeneity: $I^2 = 62\%$ , $\tau$	<sup>2</sup> = 0.4	972, p	= 0.01				-6 -4 -2 0 2 4	6		-	
C	Study	Total	Mean	befor SI	) Tota	Mean	after SD	Mean Difference	MD	95%-	-ci w	eight
	Gravvanis 2021	63	9.94	11.930	63	7.90	8.8500		- 2.04	[-1.63; 5.7	71]	4.1%
	Asbach 2020	60	7.08	2.470	0 60	5.07	1.9700		2.01	[ 1.21; 2.8	31] 541	9.7%
	Loh 2018	36	0.00 4.32	2.090	) 36 ) 15	3.48	2.2100		0.62	[-0.30; 1.5	54J 391	9.5% 7.0%
	Lenzini 2019	42	3.53	1.410	32	2.85	1.1400	-	0.68	[ 0.10; 1.2	26] 1	0.1%
	Jiang 2016	99	10.61	3.790	99	5.90	2.0500		4.71	[ 3.86; 5.5	56]	9.7%
	Ceccoli 2013 Solouni 2012	40	8.60	3.560	) 40	6.64	2.1800		1.96	[0.67; 3.2	25]	8.8%
	Rossi 2012	9 46	9.90	2.300	, g ) 46	5.20 7.85	2.3400		- 4.70	[ 2.54: 5 P	53] 541	1.5% 8.2%
	Pliz 2012	10	7.14	2.830	0 10	4.62	1.5700		2.52	[ 0.51; 4.5	53]	7.1%
	Maniero 2012 Rossi 1995	31 14	12.42 7.22	1.370 2.190	) 31 ) 14	8.00 3.99	1. <b>160</b> 0 1.8000		4.42 3.23	[ 3.79; 5.0 [ 1.75; 4.7	05] 1 71]	0.0% 8.3%
	Random effects model Heterogeneity: $l^2$ = 92%, $\tau^2$	<b>465</b> = 2.21	174, p <	< 0.01	455			-6 -4 -2 0 2 4	2.67	[ 1.73; 3.6	62] 10	0.0%
D	Random effects model Heterogeneity: $l^2 = 92\%$ , $\tau^2$ Study	465 = 2.21 Total	174, p < Mean	0.01 before SD	455 Total	Mean	after SD	-6 -4 -2 0 2 4 Mean Difference	2.67 6 MD	[1.73; 3.6 ) §	62] 10 95%-C	0.0%
D	Random effects model Heterogeneity: / <sup>2</sup> = 92%, τ <sup>2</sup> Study Gravvanis 2021	<b>465</b> = 2.21 Total 63	174, p < <b>Mean</b> 47.93	0.01 before SD	455 Total 63	<b>Mean</b> 51.17	after SD 18.2500	-6 -4 -2 0 2 4 Mean Difference	2.67 6 MD -3.24	[1.73; 3.6 ) 9	52] 10 5%-C 2.97	0.0% I Weig
D	Random effects model Heterogeneity: J <sup>2</sup> = 92%, x <sup>2</sup> Study Gravvanis 2021 Asbach 2020	<b>465</b> <sup>2</sup> = 2.21 <b>Total</b> 63 60	174, p < <b>Mean</b> 47.93 54.40	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> </ul>	<b>455</b> <b>Total</b> 63 60	<b>Mean</b> 51.17 61.16	after SD 18.2500 31.2900	-6 -4 -2 0 2 4 Mean Difference	2.67 6 MD -3.24 -6.76	[1.73; 3.6 ) 9 § [-9.45; 3 [-17.12;	52] 10 95%-C 2.97 3.60	0.0% 1 Weig ] 15.1 ] 11.1
D	Random effects model Heterogeneity: I <sup>2</sup> = 92%, t <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Adolf 2020	<b>465</b> = 2.21 <b>Total</b> 63 60 36	174, p < Mean 47.93 54.40 69.41 29.25	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8202</li> </ul>	455 Total 63 60 36	Mean 51.17 61.16 66.32	after SD 18.2500 31.2900 30.2300	-6 -4 -2 0 2 4 Mean Difference	2.67 6 MD -3.24 -6.76 3.09	[ 1.73; 3.6	52] 10 55%-C 2.97 3.60 19.28	0.0%
D	Random effects model Heterogeneity: J <sup>2</sup> = 92%, τ <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016	<b>465</b> = 2.21 <b>Total</b> 63 60 36 15 59	Mean 47.93 54.40 69.41 22.66 21.42	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>15.6500</li> </ul>	455 Total 63 60 36 15 59	Mean 51.17 61.16 66.32 25.75 42.72	after SD 18.2500 31.2900 30.2300 8.5800 17.4000	-6 -4 -2 0 2 4 Mean Difference	2.67 6 MC -3.24 -6.76 3.09 -3.09 -21.30	[1.73; 3.6 [-9.45; [-17.12; [-13.10; [-8.65; [-27.27]	<b>52] 10</b> <b>95%-C</b> 2.97 3.60 19.28 2.47 -15.33	0.0%
D	Random effects model Heterogeneity: J <sup>2</sup> = 92%, τ <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013	<b>465</b> = 2.21 <b>Total</b> 63 60 36 15 59 40	Mean 47.93 54.40 69.41 22.66 21.42 59.85	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>15.6500</li> <li>39.9000</li> </ul>	<b>455</b> <b>Total</b> 63 60 36 15 59 40	Mean 51.17 61.16 66.32 25.75 42.72 64.84	after SD 18.2500 31.2900 30.2300 8.5800 17.4000 29.9300	-6 -4 -2 0 2 4 Mean Difference	2.67 6 -3.24 -6.76 3.09 -3.09 -21.30 -4.99	[1.73; 3.6 [-9.45; 6 [-9.45; 6 [-17.12; 9 [-13.10; 9 [-8.65; 9 [-27.27; 9 [-20.45;	<b>52] 10</b> <b>5%-C</b> 2.97 3.60 19.28 2.47 -15.33 10.47	0.0%
D	Random effects model Heterogeneity: J <sup>2</sup> = 92%, t <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012	<b>465</b> = 2.21 <b>Total</b> 63 60 36 15 59 40 46	Mean 47.93 54.40 69.41 22.66 21.42 59.85 44.60	0.01 <b>before</b> <b>SD</b> 17.3300 26.3900 39.2800 6.8700 15.6500 39.9000 27.3000	<b>455</b> <b>Total</b> 63 60 36 15 59 40 46	Mean 51.17 61.16 66.32 25.75 42.72 64.84 46.50	after SD 18.2500 31.2900 30.2300 8.5800 17.4000 29.9300 22.2000	-6 -4 -2 0 2 4 Mean Difference	2.67 6 -3.24 -6 3.09 -21.30 -4.99 -1.90	[ <b>1.73</b> ; <b>3.6</b> <b>1</b> [ -9.45; <b>3</b> [-17.12; <b>4</b> [ -9.45; <b>5</b> [-17.12; <b>4</b> [ -8.65; <b>5</b> [-27.27; <b>5</b> [-20.45; <b>6</b> [-12.07;	<b>52] 10</b> <b>55%-C</b> 2.97 3.60 19.28 2.47 -15.33 10.47 8.27	0.0% <b>Weig</b> 15.3
D	Random effects model Heterogeneity: J <sup>2</sup> = 92%, τ <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Acidf 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Piz 2012 Maniero 2022	<b>465</b> = 2.21 <b>Total</b> 63 60 36 15 59 40 46 10 21	Mean 47.93 54.40 69.41 22.66 21.42 59.85 44.60 82.29	e 0.01 <b>before</b> <b>SD</b> 17.3300 26.3900 39.2800 6.8700 15.6500 39.9000 27.3000 59.1000	455 Total 63 60 36 15 59 40 46 10	Mean 51.17 61.16 66.32 25.75 42.72 64.84 46.50 102.74	after SD 18.2500 31.2900 30.2300 8.5800 17.4000 29.9300 22.2000 55.6100 21.000	-6 -4 -2 0 2 4 Mean Difference	2.67 6 -3.24 -6.76 -3.09 -3.09 -21.30 -4.99 -1.90 -20.45	[1.73; 3.6 [1.73; 3.6 [-9.45; 5 [-17.12; 9 [-13.10; 9 [-8.65; 0 [-27.27; 9 [-20.45; 0 [-20.45; 0 [-12.07; 5 [-70.75; 0 [-41.57]	<b>52] 10</b> <b>55%-C</b> 2.97 3.60 19.28 2.47 -15.33 10.47 8.27 29.85	0.0%
D	Random effects model Heterogeneity: J <sup>2</sup> = 92%, τ <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Addl 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Piiz 2012 Maniero 2012	<b>465</b> = 2.21 <b>Total</b> 63 60 36 15 59 40 46 10 31	Mean 47.93 54.40 69.41 22.66 21.42 59.85 44.60 82.29 34.00	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>15.6500</li> <li>39.9000</li> <li>27.3000</li> <li>59.1000</li> <li>21.0000</li> </ul>	455 Total 63 60 36 15 59 40 40 40 10 31	Mean 51.17 61.16 66.32 25.75 42.72 64.84 46.50 102.74 38.00	after SD 18.2500 31.2900 30.2300 8.5800 17.4000 29.9300 22.2000 55.6100 21.0000	-6 -4 -2 0 2 4 Mean Difference	2.67 6 -3.24 -6.76 3.09 -3.09 -21.30 -4.99 -1.90 -20.45 -4.00	[1.73; 3.6 [-9.45; [-17.12; -17.12; -1.13.10; -1.2.65; -1.2.77; -1.2.07; -1.2.	<b>95%-C</b> 2.97 3.60 19.28 2.47 -15.33 10.47 8.27 29.85 6.45	00.0%
D	Random effects model Heterogeneity: <i>I</i> <sup>2</sup> = 92%, <i>r</i> <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Piiz 2012 Maniero 2012 Random effects model Heterogeneity: <i>I</i> <sup>2</sup> = 72%, <i>r</i> <sup>2</sup>	<b>465</b> = 2.21 <b>Total</b> 63 60 36 15 59 40 46 10 31 <b>360</b> = 42.10	<b>Mean</b> 47.93 54.40 69.41 22.66 21.42 59.85 44.60 82.29 34.00	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>15.6500</li> <li>39.9000</li> <li>27.3000</li> <li>59.1000</li> <li>21.0000</li> <li>&lt;0.01</li> </ul>	455 Total 63 60 36 15 59 40 40 40 10 31 31 <b>360</b>	Mean 51.17 61.16 66.32 25.75 42.72 64.84 46.50 102.74 38.00	after SD 18.2500 30.2300 8.5800 17.4000 29.9300 22.2000 55.6100 21.0000	-6 -4 -2 0 2 4 Mean Difference	2.67 6 -3.24 -6.76 3.09 -3.09 -20.45 -1.90 -20.45 -4.00 -6.32	[1.73; 3.6 [1.73; 3.6 [-9.45; 5 [-17.12; 9 [-1.310; 9 [-8.65; 9 [-27.27; 9 [-20.45; 9 [-20.45; 9 [-20.45; 9 [-20.45; 9 [-70.75; 9 ]-14.45; 2 [-11.94;	<b>52] 10</b> <b>95%-C</b> 2.97 3.600 19.28 2.47 10.47 8.27 29.85 6.45 <b>-0.70</b>	0.0% <b>Weig</b> 1 15.4 1 11.1 1 16.4 1 16.4 1 16.4 1 11.1 1 11.1 1 11.1 1 11.1 1 100.0
D	Random effects model           Heterogeneity: J <sup>2</sup> = 92%, τ <sup>2</sup> Study           Gravvanis 2021           Asbach 2020           Loh 2018           Jiang 2016           Ceccoli 2013           Rossi 2012           Maniero 2012           Random effects model           Heterogeneity: I <sup>2</sup> = 72%, τ <sup>2</sup> Study	<b>465</b> <b>Total</b> 63 60 36 15 59 40 40 46 10 31 <b>360</b> = 42.1(	<b>Mean</b> 47.93 54.40 69.41 22.66 21.42 59.85 44.60 82.29 34.00 075, <i>p</i> -	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>15.6500</li> <li>27.3000</li> <li>27.3000</li> <li>21.0000</li> <li></li> <li></li></ul>	455 Total 63 60 36 15 59 40 46 10 31 360	Mean 51.17 61.16 66.32 25.75 42.72 64.84 46.50 102.74 38.00	after SD 18.2500 31.2900 30.2300 8.5800 17.4000 29.9300 22.2000 55.6100 21.0000 after SD	-6 -4 -2 0 2 4 Mean Difference	2.67 6 -3.24 -6.76 3.09 -3.09 -21.30 -21.30 -20.45 -4.90 -20.45 -4.00 -20.45 -4.00 -0 M	[1.73; 3.6 [1.73; 3.6 [-9.45; [-13.10; [-13.10; [-20.45; [-12.07; [-20.45; [-12.07; [-70.75; [-70.75; [-11.94; D 99	<b>52] 10</b> <b>95%-C</b> 2.97 3.970 19.28 2.47 -15.33 10.47 8.27 29.85 6.45 -0.70 <b>5%-C</b>	0.0% (1 Weig (1 15.) (1 11.) (1 11.) (1 12.) (1 12.) (1 11.) (1 11.) (1 11.) (1 11.) (1 10.) (1 Weig (1 Weig (1 10.) (1 10.
E	Random effects model Heterogeneity: J <sup>2</sup> = 92%, τ <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Pliz 2012 Maniero 2012 Random effects model Heterogeneity: I <sup>2</sup> = 72%, τ <sup>2</sup> Study subtype = FN Loh 2018	465 = 2.21 Total 63 60 36 15 59 40 40 40 31 360 = 42.11 Tota	<b>Mean</b> 47.93 54.40 69.41 22.66 21.42 59.85 34.00 075, <i>p</i> 4 <b>ii Mea</b>	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>15.6500</li> <li>39.9000</li> <li>27.3000</li> <li>21.0000</li> <li>21.0000</li> <li>a.0.01</li> <li>befor</li> <li>befor</li> <li>n</li> <li>SI</li> </ul>	455 Total 63 60 36 15 59 40 46 10 31 360 6 0 Tota	Mean 51.17 61.16 66.32 25.75 42.72 64.84 46.50 102.74 38.00	after SD 18.2500 31.2900 30.2300 8.5800 17.4000 29.9300 22.2000 55.6100 21.0000 21.0000	-6 -4 -2 0 2 4 Mean Difference	2.67 6 -3.24 -6.76 3.05 -3.05 -3.05 -20.45 -4.00 -20.45 -4.00 -6.32 0 MI	[1.73; 3.6 [-9.45; [-9.45; [-17.12; [-13.10; [-3.66; ]-27.27; [-20.45; ]-20.45; ]-20.45; ]-20.45; ]-20.45; ]-14.45; 2 [-11.94; D 9: (-0.00)	<b>52] 10</b> <b>55%-C</b> 2.97 3.60 19.28 2.47 10.47 8.27 29.85 6.45 <b>-0.70</b> <b>5%-C</b>	0.0% i Wei 1 15.3 1
E	Random effects model Heterogeneity: J <sup>2</sup> = 92%, t <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Acddf 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Random effects model Heterogeneity: J <sup>2</sup> = 72%, t <sup>2</sup> Study subtype = FN Loh 2018 Ceccoli 2013	465 465 1 = 2.21 Total 63 60 36 15 59 40 40 40 10 31 360 9 = 42.11 Total 11 41 41 41 41 41 41 41 41 41	174, p < Mean 47.93 54.40 69.41 22.66 21.42 59.85 44.60 82.29 34.00 075, p < 1 Mea 5 1.00 0 0.8	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>15.6500</li> <li>39.9000</li> <li>27.3000</li> <li>27.3000</li> <li>21.0000</li> <li>21.0000</li> <li>40.01</li> <li>befor</li> <li>n</li> <li>SI</li> <li>9</li> <li>0.200</li> <li>4</li> <li>0.150</li> </ul>	455 Total 63 60 36 15 59 40 46 10 31 <b>360</b> <b>6</b> <b>6</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b>	Mean 51.17 61.16 66.32 25.75 42.72 64.84 402.74 38.00	after SD 18.2500 31.2900 8.5800 17.4000 29.9300 22.2000 55.6100 21.0000 after SD 6.0.28000 0.1600	-6 -4 -2 0 2 4 Mean Difference	2.67 6 MD -3.24 -6.76 3.09 -21.33 -4.99 -20.45 -4.00 -20.45 -4.00 -0.10 0 M	[1.73; 3.6 [-9.45; [-9.45; [-17.12; -[-13.10; [-8.65; ]-[-2.07; -[-20.45; -[-20.45; -[-11.94; -[-11.	<b>52] 10</b> <b>5%-C</b> 2.97 3.60 19.28 2.47 15.33 10.47 8.27 <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.6</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b> <b>7.7</b>	10.0% i Weig ] 15.: ] 11.: ] 16. ] 16.: ] 16.: ] 11.: ] 11.: ] 11.: ] 100.: I Weig ] 11.: ] 19.0
E	Random effects model           Heterogeneity: J <sup>2</sup> = 92%, τ <sup>2</sup> Study           Gravvanis 2021           Asbach 2020           Loh 2018           Jiang 2016           Ceccoli 2013           Rossi 2012           Maniero 2012           Random effects model           Heterogeneity: I <sup>2</sup> = 72%, τ <sup>2</sup> Study           subtype = FN           Loh 2018           Salcuni 2012	465 = 2.21 Total 63 60 36 15 59 40 46 10 31 360 = 42.1( Total 11 44 44 44 44 44 44 44 44 44	<pre>I74, p ≤ Mean 47.93 54.40 69.41 22.66 21.42 59.85 44.60 075, p ≤ I Mea 5 1.00 0 0.88 5 0.66</pre>	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>15.6500</li> <li>27.3000</li> <li>27.3000</li> <li>21.0000</li> <li>4.000</li> <li>4.0.150</li> <li>9.0.60</li> </ul>	455 Total 63 60 36 15 59 40 40 31 360 0 11 0 11 0 2 4 0 4 0 11 10 10 10 10 10 10 10 10 10	Mean 51.17 61.16 66.32 25.75 42.72 42.72 42.72 42.72 42.72 42.74 46.50 102.74 38.00 102.74 38.00	after SD 31.2900 8.5800 22.2000 55.6100 22.2000 55.6100 21.0000 6.0.2800 6.0.2800 6.0.2800 6.0.600	-6 -4 -2 0 2 4 Mean Difference	2.67 6 -3.24 -6.76 -3.09 -21.33 -4.99 -20.45 -4.90 -20.45 -4.90 -20.45 -4.00 -20.45 -4.00 -0.20 -0.0 0 -0.2 -0.0 0.0.0	[1.73; 3.6 [1.73; 3.6 [-9.45; 5 [-17.12; 9 [-13.10; 9 [-8.65; 9 [-20.45; 9 [-20.45; 9 [-20.45; 9 [-20.45; 9 [-12.07; 5 [-70.75; 9 [-14.45; 2 [-11.94; D 99; 14 [-0.11; 0 [-0.07;	52] 10 55%-C 2.97 3.60 19.28 2.47 15.33 10.47 8.27 6.45 6.45 <b>-0.70</b> 5%-Cl 0.433 0.03 0.03 0.08	10.0% i Weig ] 15 ] 11 ] 16 ] 16 ] 16 ] 11 ] 1 ]
E	Random effects model Heterogeneity: J <sup>2</sup> = 92%, t <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Pliz 2012 Maniero 2012 Random effects model Heterogeneity: J <sup>2</sup> = 72%, t <sup>2</sup> Study subtype = FN Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: J <sup>2</sup> = 80%, t	465 = 2.21 Total 63 60 36 59 40 40 40 40 31 360 31 360 31 360 31 360 31 360 31 31 360 31 31 360 31 31 360 31 31 31 31 31 31 31 31 31 31	<b>Mean</b> 47.93 54.40 69.41 21.42 59.85 44.60 075, <i>p</i> < 075, <i>p</i> < 1 <b>Mea</b> 5 1.0,0 0 0.88 5 0.6 0 01183, <i>p</i>	<ul> <li>c. 0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>39.2800</li> <li>39.9000</li> <li>27.3000</li> <li>c. 0.01</li> <li>befor</li> <li>n</li> <li>Si</li> <li>9 0.200</li> <li>4 0.150</li> <li>9 0.000</li> <li>&lt; 0.01</li> </ul>	4555 Total 63 60 36 15 59 40 46 10 31 360 • • • • • • • • • • • • •	Mean 51.17 66.32 25.75 64.84 46.50 02.74 38.00 I Mean 5 0.83 5 0.68 9	after SD 18.2500 31.2900 30.2300 29.300 77.4000 29.300 55.6100 21.0000 55.6100 21.0000 55.6100 21.0000 55.61000 55.6100 55.6100 55.6100 55.6100 55.6100 55.6100 55.6100 55.6100 55.61000 55.61000 55.6100000000000000000000000000000000000	-6 -4 -2 0 2 4 Mean Difference	2.67 6 ML -3.24 -6.76 3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.06 -3.02 -0.0 0 0.00 0.00	[1.73; 3.6 [-9.45; 3 [-17.12; 9 [-8.65; 9 [-20.45; 9 [-20.45;	52] 10 55%-C 2.97 3.60 19.28 2.47 -15.33 10.47 8.27 29.85 6.45 -0.70 5%-Cl 0.433 0.03 0.038 0.22]	0.0%   Wei   15   11   15   16   16   15   16   16   11   16   11   16   11   11   10   11   10   10   10   10   10   10   10   11   10   11   10   11   10
E	Random effects model Heterogeneity: $J^2 = 92\%$ , $\tau^2$ Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Pliz 2012 Maniero 2012 Random effects model Heterogeneity: $I^2 = 72\%$ , $\tau^2$ Study subtype = FN Loh 2018 Ceccoli 2013 Random effects model Heterogeneity: $I^2 = 80\%$ , $\tau^2$ Study	$\begin{array}{c} 465\\ 465\\ 1 = 2.21\\ \hline \mbox{Total} \\ 63\\ 60\\ 36\\ 15\\ 59\\ 40\\ 10\\ 31\\ 31\\ 36\\ 10\\ 31\\ 31\\ 36\\ 10\\ 31\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 1$	I74, p <	<ul> <li>a. 0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>15.6500</li> <li>59.1000</li> <li>21.0000</li> <li>a. 0.01</li> <li>befor n SI</li> <li>9 0.2000</li> <li>a. 0.01</li> <li>befor n SI</li> <li>9 0.2000</li> <li>a. 0.01</li> <li>befor a SI</li> <li>a. 0.01</li> <li>befor a SI</li> <li>a. 0.01</li> <li>befor a SI</li> <li>befor a SI</li> <li>befor a SI</li> <li>a. 0.01</li> <li>befor a SI</li> <li>c. 0.01</li> </ul>	455 Total 63 66 15 59 40 46 10 31 360 • • • • • • • • • • • • •	Mean 51.17 61.16 66.32 25.75 42.72 44.84 46.50 102.74 38.00 102.74 38.00 102.74 38.00 102.74 38.00 102.74 38.00 102.74 38.00 102.74 5 0.833 5 0.69 5 1.09	after SD 31.2900 30.2300 30.2300 30.2300 30.2300 22.2000 55.6100 22.2000 55.6100 22.2000 55.6100 21.0000 6.0.1600 0.0600 0.0600 0.0600 0.0600	-6 -4 -2 0 2 4 Mean Difference	2.67 6 MED -3.24 -6.73 20 -21.30 -21.30 -21.30 -21.30 -21.30 -21.30 -21.30 -21.30 -21.30 -21.30 -21.45 -20.45 -3.00 -2.20 -4.57 -2.20 -2.2	[1.73; 3.6 [1.73; 3.6 [-9.45; 5] [-17.12; 9] [-8.65; 9] [-20.45; 9] [-20.45;	<b>52] 10</b> <b>55%-C</b> 2.97 3.60 19.28 2.47 15.33 10.47 8.27 29.85 6.45 <b>-0.70</b> <b>5%-C</b> 0.433 0.08 0.22] 0.12 <sup>2</sup>	0.0% il Weiş ] 15.3, ] 11.1; ] 16.4; ] 16.4; ] 16.4; ] 11.1; ] 11.1; ] 11.1; ] 11.1; ] 11.1; ] 11.1; ] 11.1; ] 11.1; ] 11.2; ] 11.4; ] 14.4; ] 14.4;
E	Random effects model Heterogeneity: $l^2 = 92\%$ , $\tau^2$ Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Pliz 2012 Maniero 2012 Random effects model Heterogeneity: $l^2 = 72\%$ , $\tau^2$ Study subtype = FN Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: $l^2 = 80\%$ , $\tau^2$ subtype = LS Loh 2018 Ceccoli 2013	465 = 2.21 Total 63 60 360 315 59 40 40 31 310 310 310 310 310 310 310	Mean 47.93 54.40 69.41 22.66 9.41 22.66 9.41 22.62 34.00 075, <i>ρ</i> + 11 Mea 5 1.00 0 0.88 5 0.66 0 0 1183, <i>ρ</i> 5 1.00 0 0.9	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>39.9000</li> <li>27.3000</li> <li>21.0000</li> <li>0.01</li> <li>befor</li> <li>n</li> <li>SS</li> <li>9.0.200</li> <li>4.0.150</li> <li>9.0.000</li> <li>&lt; 0.01</li> <li>a.152</li> <li>a.162</li> <li>a.162</li> <li>a.162</li> <li>a.162</li> <li>a.162</li> <li>b.162</li> <li>a.162</li> <li>a.162</li> <li>b.162</li> <li>a.162</li> <li>a.162</li> <li>b.162</li> <li>b.170</li> <li>b.162</li> <li>b.160</li> </ul>	455 Total 63 60 36 59 40 46 10 31 360 0 12 61 0 12 61 61 63 60 36 60 31 31 36 60 60 31 31 36 60 60 60 60 60 60 60 60 60 6	Mean 51.17 61.16 66.32 25.75 42.72 64.84 46.50 102.74 38.00 102.74 38.00 102.74 38.00 102.74 38.00 102.74 38.00 102.74 38.00 102.74 38.00 102.74 102.75 10.75 100.7	after SD 16.2500 31.2900 30.2300 29.9300 22.2000 55.6100 55.6100 55.6100 55.6100 0.0000 0.0000 0.0000 0.0000 0.0000	-6 -4 -2 0 2 4 Mean Difference	2.67 6 6 MLC -3.24 -6.75 3.05 -3.05	[1.73; 3.6 [1.73; 3.6 [-9.45; 5 [-17.12; 9 [-3.10; 9 [-3.10; 9 [-20.45; 9 [-20.45;	<b>52] 10</b> <b>55%-C</b> 2.97 3.600 19.28 2.47 <b>15.33</b> 10.47 <b>29.85</b> <b>6.45</b> <b>-0.70</b> <b>5%-C</b> <b>0.43</b> 0.03 0.08 0.22] 0.12 <b>-0.08</b>	0.0% il Weig [ 15.; ] 15.; ] 15.; ] 7.; ] 16.; ] 16.; ] 16.; ] 17.; ] 11.; ] 1.; ]
E	Random effects model Heterogeneity: J <sup>2</sup> = 92%, t <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Adolf 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Piiz 2012 Maniero 2012 Random effects model Heterogeneity: J <sup>2</sup> = 72%, t <sup>2</sup> Study subtype = FN Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: J <sup>2</sup> = 80%, t subtype = LS Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: J <sup>2</sup> = 80%, t	465 = 2.21 Total 63 60 36 15 59 40 46 10 31 360 46 40 46 40 46 40 46 40 46 40 46 40 46 40 46 40 46 40 46 40 46 40 46 46 46 46 46 46 46 46 46 46	<b>Mean</b> 47.93 554.40 69.41 22.66 59.85 44.60 075, <i>ρ</i> + <b>1 Mea</b> 5 1.00 0 0.8 5 0.6 0 0 0183, <i>ρ</i> 5 1.00 0 0.9 5 1.00	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>6.8700</li> <li>15.6500</li> <li>27.3000</li> <li>21.0000</li> <li>0.01</li> <li>befor n Si</li> <li>9.0,200</li> <li>4.0,150</li> <li>9.0,000</li> <li>&lt;0.01</li> <li>a befor n Si</li> <li>9.0,200</li> <li>&lt;0.01</li> </ul>	455 Total 63 60 36 15 59 40 46 10 31 360 0 46 61 0 46 61 0 46 61 61 62 63 60 60 60 60 60 60 60 60 60 60	Mean 51.17 61.16 66.32 25.75 42.72 64.84 46.50 102.74 38.00 1 Mean 5 0.83 0 0.88 5 0.69 5 1.09 1 .10 5 0.91 1 .10 5 0.83 1 .10 1	after SD 18.2500 8.5800 8.5800 22.2000 21.0000 after SD 4.0.2800 0.1600 0.0600 0.0600 0.1700 0.0700	-6 -4 -2 0 2 4 Mean Difference -60 -40 -20 0 20 40 60 Mean Difference	2.67 6 MLC -3.24 -6.76 -3.26 -3.26 -3.26 -3.26 -3.26 -3.26 -3.26 -3.26 -3.26 -3.26 -3.26 -3.26 -3.26 -3.26 -3.24 -3.24 -3.24 -3.24 -3.24 -3.24 -3.24 -3.24 -3.24 -3.24 -3.24 -3.24 -3.24 -3.24 -3.26 -3.24 -3.24 -3.24 -3.26 -3.24 -3.24 -3.24 -3.26 -	[1.73; 3.6 [1.73; 3.6 [-9.45; 3 [-17.12; 9 [-8.65; 9 [-20.45; 9 [-20.45;	<b>52] 10</b> <b>55%-C</b> <b>2.97</b> <b>3.928</b> <b>2.47</b> <b>15.33</b> <b>2.47</b> <b>15.33</b> <b>2.47</b> <b>15.33</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.45</b> <b>6.008</b> <b>0.003</b> <b>0.008</b> <b>0.022</b> <b>0.122</b> <b>0.122</b> <b>0.123</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b> <b>0.125</b>	00.0% (I Weig [] 15; ] 11; ] 11; ] 12; ] 13; ] 14; ] 14; ] 14; ] 14; ] 14; ] 14; ] 15; ] 16; ] 11; ] 16; ] 16;
E	Random effects model Heterogeneity: $l^2 = 92\%$ , $\tau^2$ Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Maniero 2012 Random effects model Heterogeneity: $l^2 = 72\%$ , $\tau^2$ Study subtype = FN Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: $l^2 = 80\%$ , $\tau^2$ subtype = LS Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: $l^2 = 80\%$ , $\tau^2$	$\begin{array}{c} 465\\ + 2.21\\ \hline \\ \hline$	<b>Mean</b> 47.93 54.40 69.41 22.62 59.85 44.60 075, <i>p</i> - <b>il Mea</b> 5 1.00 0 0.83 5 0.60 0 11183, <i>p</i> 5 0.80 0 0.93 5 0.80 0 0.93 5 0.80	<ul> <li>a. 0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>39.9000</li> <li>21.0000</li> <li>a. 0.01</li> <li>befor</li> <li>n</li> <li>befor</li> <li>n</li> <li>s0.01</li> <li>befor</li> <li>n</li> <li>s0.01</li> <li>befor</li> <li>a. 0.01</li> <li>befor</li> <li>a. 0.01</li> <li>befor</li> <li>a. 0.01</li> <li>befor</li> <li>a. 0.01</li> <li>befor</li> <li>befor</li> <li>a. 0.01</li> <li>befor</li> <li>befor</li> <li>a. 0.01</li> <li>befor</li> <li></li></ul>	455 Total 63 60 36 59 40 46 10 31 <b>360</b> <b>9</b> <b>7</b> <b>7</b> <b>6</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b> <b>7</b>	Mean 51.17 61.16 66.32 25.75 64.84 46.50 102.74 38.00 1 Mean 5 0.83 5 0.83 5 0.83 5 0.69 1 1.10 5 1.00 5 1.00 5 1.01	after SD 18.2500 17.4000 22.2000 21.0000 after SD 0.2800 0.0600 0.0600 0.0600 0.0700	-6 -4 -2 0 2 4 Mean Difference -60 -40 -20 0 20 40 60 Mean Difference	2.67 6 6 MLC -3.24 -6.77 3.05 -3.05	[1.73; 3.6 [1.73; 3.6 [-9.45; 5 [-17.12; 9 [-3.10; 9 [-3.10; 9 [-20.45; 9 [-20.45;	52] 10 55%-C 2.97 3.60 19.28 2.47 -15.33 6.45 -0.70 55%-Cl 0.43 0.08 0.02 0.122 -0.08 0.02	0.0% i Wei ] 15. ] 11. ] 7. ] 16. ] 7. ] 16. ] 1. ] 10. I Wei ] 11. ] 10. I Wei ] 1. ]
E	Random effects model Heterogeneity: $J^2 = 92\%, \tau^2$ Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Piiz 2012 Maniero 2012 Random effects model Heterogeneity: $J^2 = 72\%, \tau^2$ Study subtype = FN Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: $J^2 = 80\%, \tau^2$ subtype = LS Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: $J^2 = 63\%, \tau^2$	465 = 2.21 Total 63 60 36 59 40 10 31 360 = 42.1( Tota 11 44 45 41 44 45 41 12 12 12 12 12 12 12 12 12 12 12 12 12	<b>Mean</b> 47.93 54.40 22.66 69.41 22.66 69.41 22.67 44.60 82.29 34.00 075, <i>p</i> - <b>6</b> 0 075, <i>p</i> - <b>6</b> 0 0.88 5 0.66 0 0.088 5 0.08 0 0 0.083, <i>p</i> 9 0 00000, <i>p</i> 0	<ul> <li>0.01</li> <li>before SD</li> <li>17.3300</li> <li>26.3900</li> <li>39.2800</li> <li>6.8700</li> <li>39.9000</li> <li>21.0000</li> <li>0.01</li> <li>befor</li> <li>n</li> <li>befor</li> <li>n</li> <li>befor</li> <li>n</li> <li>befor</li> <li>a</li> <li>a</li> <li>a</li> <li>a</li> <li>a</li> <li>a</li> <li>a</li> <li>b</li> <li>a</li> <li>b</li> <li>a</li> <li>a</li> <li>b</li> <li>a</li> <li>a<!--</td--><td>455 Total 63 60 36 15 59 40 10 360 <b>D</b> Total <b>360</b> <b>D</b> Total <b>360</b> <b>D</b> <b>Total</b> <b>360</b> <b>D</b> <b>1</b> <b>1</b> <b>3</b> <b>1</b> <b>3</b> <b>1</b> <b>1</b> <b>3</b> <b>1</b> <b>1</b> <b>3</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b></td><td>Mean 51.17 61.16 66.32 25.75 44.84 46.50 102.74 38.00 1 Mean 5 0.83 0 0.88 5 0.69 1 1.10 5 0.91</td><td>after SD 18.2500 17.4000 22.2000 21.0000 after 5.6100 21.0000 0.1600 0.0600 0.0600 0.0700</td><td>-6 -4 -2 0 2 4 Mean Difference -60 -40 -20 0 20 40 60 Mean Difference</td><td>2.67 6 MLC -3.24 -6.73 3.05 -3</td><td>[1.73; 3.6 [1.73; 3.6 [-9.45; 5 [-17.12; 9 [-8.65; 9 [-20.45; 9 [-20.45;</td><td>52] 10 55%-C 2.97 3.60 19.28 2.47 15.33 10.47 8.27 29.85 6.45 6.45 6.45 6.45 6.45 0.43 0.03 0.02 0.122 0.08 0.06</td><td>0.0% i Wei ] 15, ] 11, ] 11, ] 11, ] 16, ] 16, ] 16, ] 11, ] 1, ] 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1</td></li></ul>	455 Total 63 60 36 15 59 40 10 360 <b>D</b> Total <b>360</b> <b>D</b> Total <b>360</b> <b>D</b> <b>Total</b> <b>360</b> <b>D</b> <b>1</b> <b>1</b> <b>3</b> <b>1</b> <b>3</b> <b>1</b> <b>1</b> <b>3</b> <b>1</b> <b>1</b> <b>3</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b> <b>1</b>	Mean 51.17 61.16 66.32 25.75 44.84 46.50 102.74 38.00 1 Mean 5 0.83 0 0.88 5 0.69 1 1.10 5 0.91	after SD 18.2500 17.4000 22.2000 21.0000 after 5.6100 21.0000 0.1600 0.0600 0.0600 0.0700	-6 -4 -2 0 2 4 Mean Difference -60 -40 -20 0 20 40 60 Mean Difference	2.67 6 MLC -3.24 -6.73 3.05 -3	[1.73; 3.6 [1.73; 3.6 [-9.45; 5 [-17.12; 9 [-8.65; 9 [-20.45; 9 [-20.45;	52] 10 55%-C 2.97 3.60 19.28 2.47 15.33 10.47 8.27 29.85 6.45 6.45 6.45 6.45 6.45 0.43 0.03 0.02 0.122 0.08 0.06	0.0% i Wei ] 15, ] 11, ] 11, ] 11, ] 16, ] 16, ] 16, ] 11, ] 1, ] 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1
E	Random effects model Heterogeneity: $I^2 = 92\%$ , $\tau^3$ Study Gravvanis 2021 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Piiz 2012 Maniero 2012 Random effects model Heterogeneity: $I^2 = 72\%$ , $\tau^2$ Study subtype = FN Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: $I^2 = 80\%$ , $\tau$ subtype = LS Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: $I^2 = 80\%$ , $\tau$ subtype = LS Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: $I^2 = 63\%$ , $\tau$ Random effects model Heterogeneity: $I^2 = 77\%$ , $\tau$ rest for subgroup different	$\begin{array}{c} 465\\ = 2.21\\ \hline\\ \mbox{Total}\\ 63\\ 60\\ 36\\ 59\\ 40\\ 10\\ 31\\ 360\\ \mbox{a}\\ 8\\ 40\\ 46\\ 10\\ 31\\ \mbox{a}\\ 8\\ 40\\ 46\\ 10\\ \mbox{a}\\ 10\\ \mbox{a}\\ 11\\ \mbox{a}\\ 42.10\\ \mbox{a}\\ 11\\ \mbox{a}\\ 12\\ \$	Mean 47.93 54.40 69.41 22.66 69.41 22.66 82.29 34.00 34.00 51.00 00.88 50.6 00 00.88 50.6 00 00.89 51.00 00.85 50.8 00 00.89 51.00 00.85 50.85 00 00.89 51.00 00.85 50.85 00 00.85 50.85 00 00 00 00 00 00 00 00 00 0	<ul> <li>c0.01</li> <li>before SD</li> <li>c17.3300</li> <li>c6.3900</li> <li>c6.3900</li> <li>c8.700</li> <li>c9.010</li> <li>c0.01</li> </ul>	455 Total 63 60 36 15 59 40 46 15 59 40 46 15 59 40 46 15 59 40 46 15 59 40 46 15 59 40 46 15 59 40 46 15 50 46 16 50 16 16 16 16 16 16 16 16 16 16	Mean 51.17 61.16 66.32 25.75 64.84 46.50 02.74 38.00 I Mean 5 0.88 5 0.088 5 0.089 5 1.09 0 1.10 5 0.91	after SD 18.2500 8.5800 29.3002 22.2000 21.0000 1.1600 0.1600 0.0600 0.0600 0.0700	-6 -4 -2 0 2 4 Mean Difference -6 -4 -2 0 2 4 Mean Difference -6 -4 -2 0 2 4	2.67 6 MCL -3.24 -6.7 3.05 -3.0	[1.73; 3.6 [1.73; 3.6 [-9.45; 5] [-17.12; 0] [-3.10; 1] [-3.10; 1] [-2.72; 0] [-20.45; 0] [-20.45; 0] [-20.45; 0] [-20.45; 1] [-20.45; 1] [-20.45; 1] [-20.45; 2] [-11.94; 2] [-11.94; 2] [-11.94; 2] [-0.11; 3] [-0.11; 3] [-0.12; 3] [-0.17; 1] [-0.10; 3] [-0.10; 4] [-0.10;	52] 10 55%-C 2.97 3.60 19.28 2.47 15.33 10.47 8.27 29.85 6.45 -0.70 55%-Cl 0.43 0.08 0.08 0.08 0.08 0.06 0.02 0.08] 0.08	0.0% (I Wei ] 15. ] 11. ] 7. ] 11. ] 16. ] 11. ] 11. ] 11. ] 11. ] 11. ] 11. ] 11. ] 12. ] 14. ] 18. ] 14. ] 18. ] 14. ] 18. ] 14. ] 18. ] 14. ] 18. ] 19. ] 19. ] 19. ] 10. ] 10. ] 10. ] 10. ] 11. ] 10. ] 11. ] 10. ] 11. ] 11. ] 11. ] 11. ] 15. ] 11. ] 15. ] 16. ] 17. ] 17. ] 17. ] 18. ] 19. ] 19. ] 19. ] 11. ] 11. ] 10. ] 11. ] 1
F	Random effects model Heterogeneity: J <sup>2</sup> = 92%, t <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Adolf 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Piiz 2012 Maniero 2012 Random effects model Heterogeneity: J <sup>2</sup> = 72%, t <sup>2</sup> Study subtype = FN Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: J <sup>2</sup> = 80%, t subtype = LS Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: J <sup>2</sup> = 80%, t subtype = LS Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: J <sup>2</sup> = 63%, t Random effects model Heterogeneity: J <sup>2</sup> = 77%, t Test for subgroup different	$\begin{array}{c} 465\\ 465\\ = 2.21\\ \hline \\ \textbf{Total}\\ \hline \\ 63\\ 60\\ 36\\ 59\\ 40\\ 40\\ 40\\ 10\\ 31\\ \hline \\ \textbf{360}\\ 0\\ 10\\ 31\\ \hline \\ \textbf{360}\\ 0\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\$	<b>Mean</b> 47.93 54.40 259.85 59.85 44.60 0075, <i>p</i> - <b>11 Mea</b> 5 1.00 0 0.88 5 1.00 0 0.93 5 1.00 0 0.00 5 1.00 5 1.00	<ul> <li>c0.01</li> <li>before SD</li> <li>c17.3300</li> <li>c2.3200</li> <li>c2.3200</li> <li>c2.3200</li> <li>c2.3200</li> <li>c2.10000</li> <lic2.10000< li=""> <li>c2.10000</li> <li>c2.10000</li></lic2.10000<></ul>	455 Total 63 60 36 15 5 9 40 46 10 31 360 7 Total 6 0 12 6 12 12 12 12 12 12 12 12 12 12	Mean 51.17 61.16 66.32 25.75 64.84 42.72 64.84 46.50 102.74 38.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 10.	after SD 18.2500 17.4000 22.2000 21.0000 after 5.6100 21.0000 0.0600 0.0600 0.0700 0.0700 after SD	-6 -4 -2 0 2 4 Mean Difference -60 -40 -20 0 20 40 60 Mean Difference -0.4 -0.2 0 0.2	2.67 6 MLC -3.24 -6.7 3.05 -0.05 -0.	[1.73; 3.6 [1.73; 3.6 [-9.45; 5 [-17.12; 9 [-3.10; 9 [-3.10; 9 [-20.45; 9 [-0.14; 5 [-0.22; 13 [-0.13; 7 [-0.17; 11 [-0.10; 9 [95]	<b>32] 10</b> <b>95%-C</b> <b>2.97</b> <b>3.60</b> <b>19.28</b> <b>2.47</b> <b>15.33</b> <b>10.47</b> <b>8.27</b> <b>29.85</b> <b>6.45</b> <b>-0.70</b> <b>5%-C</b> <b>0.43</b> <b>0.03</b> <b>0.03</b> <b>0.03</b> <b>0.03</b> <b>0.03</b> <b>0.03</b> <b>0.03</b> <b>0.03</b> <b>0.06</b> <b>0.02</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b>0.068</b> <b></b>	0.0% (  Weig   15.   11.   7.   7.   7.   7.   7.   7.   13.   16.   7.   1.   16.   7.   1.   1.
F	Random effects model Heterogeneity: $I^2 = 92\%, \tau^2$ Study Gravvanis 2021 Asbach 2020 Asbach 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Pliz 2012 Maniero 2012 Random effects model Heterogeneity: $I^2 = 72\%, \tau^2$ Study subtype = FN Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: $I^2 = 80\%, \tau$ subtype = LS Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: $I^2 = 80\%, \tau$ Random effects model Heterogeneity: $I^2 = 80\%, \tau$ Random effects model Heterogeneity: $I^2 = 63\%, \tau$ Random effects model Heterogeneity: $I^2 = 73\%, \tau$ Test for subgroup different Study Adolf 2020 Ceccoli 2013	$\begin{array}{c} 465\\ + 2.21\\ \hline \\ \hline$	Mean 47.93 54.40 69.41 22.66 69.41 22.63 59.85 59.85 59.85 59.85 59.85 51.00 0075, p - 11 Mean 51.00 00.03, p 50.85 00 00039, p 50.85 00 00039, p 1100, p 1100	<ul> <li>c0.01</li> <li>before SD 17.3300 26.3900</li> <li>c6.3900</li> <li>c6.3900</li> <li>c7.3000</li> <li>c0.01</li> <li>before n Si</li> <li>c0.01</li> <li>before n Si</li> <li>c0.01</li> <li>c0.02</li> <li>c0.02</li> <li>c0.02</li> <li>c0.03</li> <li>c0.04</li> <li>c0.04</li> <li>c0.04</li> <li>c0.05</li> <li>c0.05</li> <li>c0.04</li> <li>c0.04</li> <li>c0.05</li> <li>c0.04</li> <li>c0.04</li> <li>c0.05</li> <li>c0.05</li> <li>c0.04</li> <li>c0.05</li> <li>c0.04</li> <li>c0.04</li> <li>c0.05</li> <li>c0.04</li> <li>c0.04</li> <li>c0.04</li> <li>c0.05</li> <li>c0.04</li> <li>c0.04</li> <li>c0.05</li> <li>c0.04</li> <li>c0.04</li> <li>c0.05</li> <li>c0.05</li> <li>c0.04</li> <li>c0.04</li> <li>c0.04</li> <li></li></ul>	455 Total 63 60 36 15 59 40 46 10 31 360 0 19 0 48 60 0 19 0 48 60 0 48 60 0 31 360 0 7 0 7 0 7 10 10 10 10 10 10 10 10 10 10	Mean 51.17 61.16 66.32 25.75 64.84 442.72 64.84 46.50 102.74 38.00 1 Mean 5 0.83 0 0.88 5 0.83 0 0.88 5 0.83 0 0.88 5 0.91 1 .10 5 0.91 1 .10 5 0.91 1 .10 5 0.91 1 .10 1 .10 5 0.91 1 .10 1 .	after SD 18.2500 29.30.2300 8.5800 29.9300 29.9300 29.9300 21.0000 0.155 0.0000 0.0600 0.0600 0.07000 0.07000 0.0700000000	-6 -4 -2 0 2 4 Mean Difference -6 -4 -2 0 2 4 Mean Difference -6 -4 -2 0 2 4 Mean Difference -6 -4 -2 0 2 4 -6 -4 -2 0 0 0 0 2 4 -6 -4 -2 0 0 0 0 2 4 -6 -4 -2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	2.67 6 MEL -3.24 -6.73 20.45 -2.130 -2.040 -2.040 -0.00 -	[1.73; 3.6 [1.73; 3.6 [-9.45; 5] [-17.12; 5] [-17.12; 5] [-20.45; 5] [-12.07; 5] [-20.45; 6] [-20.45; 6] [-20.45; 6] [-20.45; 6] [-20.45; 6] [-20.45; 6] [-0.11; 6] [-0.11; 6] [-0.11; 6] [-0.11; 6] [-0.11; 6] [-0.11; 6] [-0.11; 6] [-0.12; 6] [-0.12;	52] 10 55%-CC 2.97 3.60 19.28 2.47 -15.33 2.47 -15.33 2.47 -0.70 55%-CC 0.43 0.03 0.12 0.03	00.0% (I Weig ) 15., ) 11., ) 7., ) 7., ) 16., ) 13., ) 13., 1 11., ) 11., ) 11., ) 14., 1 19., 1 19., 1 19., 1 19., 1 100, 1 100,
D E F	Random effects model Heterogeneity: J <sup>2</sup> = 92%, t <sup>2</sup> Study Gravvanis 2021 Asbach 2020 Adolf 2020 Loh 2018 Jiang 2016 Ceccoli 2013 Rossi 2012 Piiz 2012 Maniero 2012 Random effects model Heterogeneity: J <sup>2</sup> = 72%, t <sup>2</sup> Study subtype = FN Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: J <sup>2</sup> = 80%, t subtype = LS Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: J <sup>2</sup> = 80%, t subtype = LS Loh 2018 Ceccoli 2013 Salcuni 2012 Random effects model Heterogeneity: J <sup>2</sup> = 63%, t Random effects model Heterogeneity: J <sup>2</sup> = 77%, t Test for subgroup different Study Adolf 2020 Ceccoli 2013	$\begin{array}{c} 465\\ 465\\ = 2.21\\ \hline \\ \hline$	Mean 47.93 54.40 69.41 22.66 82.29 34.00 075, <i>p</i> - 1 1 <b>Mea</b> 5 1.00 0.85 5 0.6 0 0.039, <i>p</i> 1100, <i>p</i> 11	<ul> <li>c0.01</li> <li>before SD</li> <li>c17.3300</li> <li>c8.3900</li> <li>c9.2800</li> <li>c8.7000</li> <li>c9.001</li> <li>c9.0200</li> <li>c0.01</li> <li>before n SI</li> <li>9 0.2000</li> <li>c0.01</li> <li>c1.000</li> <li>c0.01</li> <li>c1.000</li> <lic1.000< li=""> <lic1.000< li=""> <li>c1.000</li> <li>c1.</li></lic1.000<></lic1.000<></ul>	455 Total 63 60 15 59 9 40 40 10 31 360 7 Total 61 0 41 61 0 41 61 61 61 61 61 61 61 61 61 6	Mean 51.17 61.16 66.32 25.75 64.84 42.72 64.84 46.50 102.74 38.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 102.74 39.00 10.0	after SD 18.2500 17.4000 22.2000 21.0000 after 5.6100 0.0600 0.0600 0.0700 0.0700 0.0700 after SD 8.1100 15.7000	-6 -4 -2 0 2 4 Mean Difference -60 -40 -20 0 20 40 60 Mean Difference -0.4 -0.2 0 0.2 Mean Difference	2.67 6 MLC -3.24 -6.73 3.05 -0.05 -0	[1.73; 3.6 [1.73; 3.6 [-9.45; 5 [-17.12; 9 [-20.45; 9 [-20.45; 9 [-20.45; 9 [-20.45; 9 [-20.45; 9 [-20.45; 9 [-20.45; 9 [-20.45; 1 [-20.47; 2 [-11.94; 2 [-11.94; 1 [-0.14; 5 [-0.22; 3 [-0.13; 7 [-0.17; 1 [-0.10; 0 95 6 [-2.74; 0 95	52] 10 55%-CC 2.97 3.60 19.28 2.47 10.47 8.27 -0.70 5%-CC 0.43 0.08 0.08 0.08 0.02 0.02 0.02 0.02 0.02 0.02 0.08 %-CC	0.0% (  Wei   15.   11.   7.   15.   7.   15.   7.   15.   7.   16.   7.   16.   7.   1.   1

FIGURE 3

Forest plots of before-treatment vs. after-treatment PA patients (A: serum calcium, B: urine calcium, C: serum PTH, D: serum 25-OHD, E: BMD of FN and LS, F: BAP).

А									
	Study	Total	Unilatera Mean SI	l D Total	Bilatera Mean SI	l Mean Difference	MD	95%-CI	Weight
	Kometani 2021	60	2 30 0 100	0 54	2 30 0 080	) <u> </u>	0.00	[-0 03· 0 03]	14.6%
	Kometani 2021	19	2.30 0.100	0 105	2.30 0.100		0.00	[-0.05; 0.05]	6.7%
	Yokomoto 2020	37	2.30 0.100	0 76	2.30 0.080		0.00	[-0.04; 0.04]	11.7%
	Tuersun 2020 Asbach 2020	76	2.30 0.130	) 80 ) 55	2.31 0.120		-0.01	[-0.05; 0.03]	10.3%
	Lim 2018	23	2.20 0.080	0 19	2.25 0.080		-0.04	[-0.10; 0.00]	6.8%
	Jiang 2016	123	2.15 0.110	0 119	2.16 0.100		-0.01	[-0.04; 0.02]	22.8%
	Petramala 2014	35	2.30 0.120	0 38	2.30 0.100		0.00	[-0.05; 0.05]	6.2%
	Rossi 2012	46	2.30 0.100	0 12	2.38 0.110	) — <u>*</u>	-0.08	[-0.15; -0.01]	3.4%
	Common effect model Heterogeneity: $l^2 = 23\%$ , $\tau$	<b>489</b> <sup>2</sup> < 0.0	001, <i>p</i> = 0.24	558			-0.02	[-0.03; 0.00]	100.0%
в			Unilator	al	Bilator	-0.1 -0.05 0 0.05 0.1			
5	Study	Total	Mean S	D Tota	I Mean S	D Mean Difference	MD	95%-CI	Weight
	Tuersun 2020	76	5.75 2.840	0 8	5.91 2.300	0	-0.16	[-0.97; 0.65]	29.4%
	Jiang 2016	123	5.06 1.980	0 11	4.86 2.400	0	0.20	[-0.36; 0.76]	34.5%
	Petramala 2014	35	5.56 2.520	0 3	3 6.87 3.510 4 10 2 100	0	-1.31	[-2.70; 0.08]	19.1%
	Rossi 2012	40	5.00 3.400	0 1.	2 4.19 2.100		- 1.47	[-0.07; 3.01]	17.0%
	Random effects model Heterogeneity: $l^2 = 60\%$ , $\tau$	<b>280</b> <sup>2</sup> = 0.4	434, <i>p</i> = 0.06	24	9		0.02	[-0.81; 0.86]	100.0%
с			Unilater	al	Bilater	-3-2-1012 N	3		
	Study	Total	Mean S	D Tota	I Mean S	D Mean Difference	MD	95%-CI	Weight
	Kometani 2021	60	6.21 3.260	0 5	1 5.89 2.110	0	0.32	[-0.68; 1.32]	12.3%
	Kometani 2021	19	6.53 1.890	0 10	5 6.11 2.950	0	0.42	[-0.60; 1.44]	12.1%
	Yokomoto 2020	37	6.74 2.530	0 70	5 6.11 3.050		0.63	[-0.44; 1.70]	11.7%
	Asbach 2020	70	7.92 2 280	0 5	5 6 80 3 110	0	1.00	[0.80, 2.56]	12.5%
	Lim 2018	23	6.52 3.230	0 1	5.17 1.980	o + 🔚	1.35	[-0.24; 2.94]	7.7%
	Jiang 2016	123	9.47 4.150	0 11	7.95 3.450	0	1.52	[ 0.56; 2.48]	12.7%
	Petramala 2014 Rossi 2012	35	4.84 2.120	0 3	3 5.33 2.130 2 8.60 3 150		-0.49 - 3.34	[-1.47; 0.49]	12.6%
	Rossi 2012	40	11.34 4.010				0.04	[ 1.00, 0.00]	4.076
	Heterogeneity: $l^2 = 59\%$ , $\tau$	$^{2} = 0.4$	121, <i>p</i> = 0.01	55	,		0.93	[ 0.30, 1.49]	100.0 %
D			Unilater	al	Bilate	-4 -2 0 2 4 al			
	Study	Total	Mean S	D Tota	I Mean S	5D Mean Difference	MD	95%-	CI Weight
	Tuersun 2020	76	45.76 16.360	0 80	50.67 24.66	00 -++	-4.91	[-11.45; 1.6	3] 19.7%
	Asbach 2020	70	49.32 22.470	0 5	57.23 36.64		-7.91	[-18.93; 3.1	1] 6.9%
	Jiang 2016	23 123	27.81 17.800	0 11	32.22 10.20		-3.75	[-13.39; 5.8	9] 57.7%
	Petramala 2014	35	53.12 41.400	0 38	3 46.13 44.39	00	- 6.99	[-12.69; 26.6	7] 2.2%
	Rossi 2012	46	44.60 27.300	0 12	2 54.40 20.40	00	-9.80	[-23.78; 4.1	8] 4.3%
	Common effect model	373		323	3	-	-4.68	[ -7.58; -1.7	7] 100.0%
	Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p =	= 0.81					-	-
Е			Unilator	al	Bilator	-20 -10 0 10 20			
	Study	Total	Mean S	D Tota	I Mean S	D Mean Difference	MD	95%-CI	Weight
	Section = LS					. 11 _			10.001
	Yokomoto 2020	37	0.97 0.217	0 70	5 0.90 0.171		- 0.08	[0.00; 0.16]	19.9%
	Random effects model	35	1.00 0.180	U 30 14	5 1.02 0.170 1		-0.02	[-0.10; 0.06]	39.6%
	Heterogeneity: $I^2 = 64\%$ , $\tau$	<sup>2</sup> = 0.0	029, p = 0.10		-		5.00		201010
	Section = FN		0.70 0.400	o -	0.00.01:-		0.00	10.00.00	20.0%
	rokomoto 2020 Petramala 2014	37	0.70 0.128	0 70	0.68 0.115		0.03	[-0.02; 0.07]	39.0% 21.4%
	Random effects model	72	0.02 0.140	114	1 0.00 0.190		0.03	[-0.05; 0.06]	60.4%
	Heterogeneity: $I^2 = 32\%$ , $\tau$	<sup>2</sup> = 0.0	005, p = 0.22		-			,	
	Random effects model	144		22	3		0.01	[-0.03; 0.06]	100.0%
	Heterogeneity: $I^2 = 33\%$ , $\tau$	$^{2} = 0.0$	005, p = 0.21	n = 0.00		-0.15-0.1-0.05_0_0.05_0.1_0	15		
	rest for subgroup difference	les: χ <sub>1</sub>	- 0.10, df = 1 (	p = 0.68	"	-0.15-0.1-0.05 0 0.05 0.1 0.	. 1 <b>D</b>		
unilateral	l vs. bilateral PA pat	ients	(A: serum	calci	um, <b>B</b> : urir	ie calcium, <b>C</b> : serum PTH	l, <b>D</b> : se	erum 25-C	DHD, E: BMD

# Discussion

We consistently found that PA patients (especially unilateral patients) were at higher risk of OP than EH subjects but the risk was reduced after medical treatment or surgery. Thus, aldosterone may affect both PTH secretion and bone metabolism.

# Direct effects of aldosterone on bone metabolism

Excess aldosterone directly affects bone formation and resorption; inhibition of the RAAS system reduces bone loss (17). The following mechanisms may explain these phenomena. The long-term oxidative stress and chronic inflammation of PA patients



may increase osteoblast and osteocyte apoptosis (35), triggering abnormal bone metabolism, secondary OP, and even fracture (36), (37). It is well known that glucocorticoids can affect bone metabolism. Recently, mineralocorticoids have also been found to be related to bone metabolism. Researchers have found that MR antagonists (MRAs) reduced the risk of fracture in patients with secondary aldosteronism (38). Beavan et al. (39) reported (in 2001) that MR existed in human osteocytes; aldosterone may thus act directly on osteocytes. Later studies showed that several genes of the mineralocorticoid pathway (NR3C2, PIK3R1, PRKCH, and SCNN1B) may affect bone strength (40).

# Aldosterone may affect bone metabolism by interacting with PTH or vitamin D

Resnick et al. (34) were the first to report elevated PTH levels in PA patients (in 1985). Many studies (14, 17, 18), (25–27, 29,

TABLE 2 Sensitivity analysis on "high quality" studies (NOS≥8).

30), (32), (33) have confirmed this. A possible bidirectional interaction between aldosterone and PTH has been suggested (6), (7). Several studies have proposed that aldosteronism may cause secondary HPT by reducing sodium and calcium reabsorption by the proximal renal tubules (26), (27), (30), (32), increasing urinary calcium excretion, and long-term calcification. This explains why PA patients tend to have higher serum calcium but lower urinary calcium levels than others. It has been suggested that, in the acute phase, regulation of PTH secretion by the RAAS system is mediated by angiotensin II (Ang II), but aldosterone may be involved in such regulation in the chronic phase (41). PTH and calcium levels both affect aldosterone secretion; however, that is not our topic here.

PA patients more commonly exhibit vitamin D deficiency than others (42); vitamin D supplementation downregulates the RASS system (43), (44). We found no significant difference in serum 25-OHD levels between PA and EH patients, but the level increased significantly in PA patients after medical treatment or surgery,

Item	N of studies	N of patients/controls	MD (95% CI)	$I^2$	P-value
PA vs. EH					
Serum calcium	4	466/532	-0.03 (-0.09, 0.03)*	84%	< 0.01
Urine calcium	3	456/350	0.76 (0.41, 1.12)	0%	0.50
Serum PTH	4	466/532	2.59(1.69, 3.50)	82%	< 0.01
Serum 25-OHD	4	466/532	-1.51 (-6.43, 3.41)	60%	0.06
Before-treatment vs. A	fter-treatment PA				
Serum calcium	7	323/323	-0.08 (-0.11, -0.05)	70%	< 0.01
Urine calcium	6	284/284	2.17 (1.70, 2.65)	0%	0.66
Serum PTH	8	354/354	3.19 (2.03, 4.36)	90%	< 0.01
Serum 25-OHD	7	305/305	-7.00 (-14.13, 0.13)*	76%	< 0.01
Unilateral vs. Bilatera	l PA				
Serum calcium	5	338/285	-0.03 (-0.04, -0.01)*	35%	0.19
Urine calcium	3	245/211	0.20 (-0.24, 0.64)	40%	0.19
Serum PTH	5	338/285	1.54 (1.04, 2.04)	0%	0.51
Serum 25-OHD	5	338/285	-4.94 (-7.87, -2.00)	0%	0.93

N, number; MD, mean difference; 95% CI, 95% Confidence Intervals; \* MD results changed after excluding "low quality" studies.

PA vs. EH         Asian         1         416/293         0.03 (0.01, 0.05)         88%         0.01         0.81           Semura claim         Asian*         2         986/276         0.07 (0.02, 1.03)         0.86         0.01         0.87         (5.1)           Seturope         5         272/293         1.29 (1.02, 1.03)         0.66         0.67         (5.1)           Seturo PTH         1. Asian         3         446/293         2.37 (1.14, 3.5)         886         0.01         0.97           2. CCLA         3         202/448         2.20 (1.16, 2.34)         556         0.11         1.89           ELISA         1         426/93         0.20 (1.62, 3.43)         -         -         -           Seturo 2.5OHD         1. Asian         3         961/293         0.16 (6.43, 4.31)         -         -         -         2.75           Seturo 2.5OHD         1. Asian         3         416/293         0.16 (6.43, 4.31)         -         -         2.75           Elicove         4         257/499         -1.115 (30.75, 8.45)         986         0.01         0.02           Elicove         7         246/24         -0.06 (4.09, -0.04)         0.56         0.26         0.26 <th>Item</th> <th>Subgroup</th> <th>N of studies</th> <th>N of patients</th> <th>MD (95% CI)</th> <th><math>I^2</math></th> <th>P-value for I<sup>2</sup></th> <th><math>\mathbf{X}^2</math></th>	Item	Subgroup	N of studies	N of patients	MD (95% CI)	$I^2$	P-value for I <sup>2</sup>	$\mathbf{X}^2$
Serun calcin harroyAira harroy3Al40230.01 (0.11, 0.02)88%0.010.11Utite calcina harroyAira23980250.07 (0.41, 1.03)0%0.071.51Serun PTD1 harroy1. Asian34160232.57 (1.14, 1.53)88%0.010.19Serun PTD1 HISA12.400172.245 (1.36, 2.57)6.15%0.010.19TISA14.20010.000 (0.12, 1.24)TISA14.20010.000 (0.12, 1.24)TISA14.20010.000 (0.12, 1.24)TISA14.20010.000 (0.12, 1.24)TISA14.20010.010 (1.25, 2.45)0.001TISA11.20072.211 (1.233)TISA22.00172.211 (1.233)TISA22.00172.211 (1.233)TISA22.00172.211 (1.233)TISA22.00172.211 (1.233)TISA22.00172.011 (1.233, 5.01)TISA22.01172.211 (1.233)TISA22.01172.211 (1.233)TISA22.01172.011432.01111TISA22.01172.011432.01143TISA22.0117	PA vs. EH							
Line calcin EmergeAim Emerge298/0780.77 (0.4.1.13)0.%0.871.81Serum PTH Europe130.40232.37 (1.4.1.59)8%0.000.13Serum PTH ELSA12.37 (1.4.1.59)8%0.010.13ELSA12.403 (1.56.2.75)8%0.010.13ELSA12.403 (1.56.2.75)8%0.010.16ELSA12.403 (1.57.4.54)7%0.010.16ELSA12.403 (1.57.4.54)7%0.010.16Air19.074 (2.23.1.66)0.16ELSA11.016 (1.57.54)9%0.010.16ELTA11.017 (2.23.1.66)9%0.010.16ELTA11.017 (2.23.1.66)9%0.010.16ELTA11.017 (2.23.1.66)9%0.010.10ELTA11.017 (2.23.1.66)9%0.010.10ELTA11.017 (2.23.1.66)9%0.010.10ELTA11.017 (2.23.1.66)9%0.010.10ELTA11.017 (2.23.1.66)9%0.010.10ELTA11.017 (2.23.1.66)9%0.010.10ELTA11.017 (2.23.1.66)0.100.100.10ELTA11.017 (2.23.1.66)0.100.100.10ELTA11.017 (2.23.1.66)0.100.100.10ELTA11	Serum calcium	Asian Europe	3 5	416/293 267/459	-0.03 (-0.11, 0.05) -0.07 (-0.13, -0.02)	88% 87%	<0.01 <0.01	0.81
Semi PTH ErrorAlam Error3416/232.7 (1.4, 3.9)8.8%.0.010.19ErrorError3220 (1.4, 2.9)5.5%0.1118.91.15.04.014.010.00 (0.10, 2.0)ELRO14.010.00 (0.12, 0.12)RIA34.012.01 (1.4, 2.9)7.6%0.07Mit34.0122.01 (1.2, 2.9)7.6%0.07Error13.014.0123.01 (1.2, 0.2)8.5%0.01Error12.00 (1.1, 5.00.7, 8.45)8.6%0.010.05ECLA220137.21 (0.2, 0.5, 8.45)8.6%0.010.05ECLA220137.21 (0.2, 0.5, 8.45)8.6%0.010.01Chror12.00 (1.1, 0.00, 8.45)9.6%0.010.010.01Chror12.02 (1.1, 0.00, 8.45)9.6%0.010.010.01Chror12.02 (1.0, 0.11)0.050.010.010.01Chror12.02 (1.0, 0.11)0.010.010.010.01Chror12.02 (1.0, 0.11)0.010.010.010.01Chror12.02 (1.0, 0.11)0.010.010.010.01Chror12.02 (1.0, 0.11)0.010.010.010.01Chror12.02 (1.0, 0.11)0.010.010.010.01Chror12.02 (1.0, 0.11)0.01 </td <td>Urine calcium</td> <td>Asian* Europe</td> <td>2 5</td> <td>398/276 273/293</td> <td>0.77 (0.42, 1.13) 1.59 (1.39, 1.80)</td> <td>0% 40%</td> <td>0.87 0.15</td> <td>15.19</td>	Urine calcium	Asian* Europe	2 5	398/276 273/293	0.77 (0.42, 1.13) 1.59 (1.39, 1.80)	0% 40%	0.87 0.15	15.19
2. ECIA328/4482.0 (1.4, 2.94)5.%0.1118.9EISA2360/1372.7 (1.04, 4.81)7.0%0.07RIA3300 (1.2, 2.23)7.1%0.01RIA3416.0330.10 (6.34, 4.11)7.0%0.01RIA3416.0330.11 (6.34, 4.11)7.0%0.01RIA2200172.24, 2.05, 3.438.9%0.01RIA2200172.24, 2.05, 3.438.9%0.01RIA2200172.24, 2.05, 3.438.9%0.01RIA2200172.24, 2.05, 3.438.9%0.01RIA2200172.24, 2.05, 3.438.9%0.01RIA22.41042.99, 9.68, 6.899.1%0.01RIA13.99, 9.99, 8.94, 8.94, 8.94, 8.949.1%0.01RIM PTH1Asian22.14142.28, 1.64, 0.27, 2.9%RIM PTH14.1412.94, 0.48, 6.89, 6.94, 9.94, 9.940.01RIM PTH14.1412.52, 1.04, 0.14, 9.940.01RIM PTH14.1412.24, 0.143, 1.7%0.01RIM PTH14.1412.24, 0.144, 1.740.14RIM PTH14.1413.24, 1.445, 0.77, 1.7%0.1RIM PTH14.1413.24, 1.445, 0.77, 1.7%0.1RIM PTH14.1413.24, 1.445, 0.74, 1.7%0.1RIM PTH14.1413.24, 1.445, 0.77, 1.7%0.1RIM PTH <td>Serum PTH</td> <td>1. Asian Europe</td> <td>3 7</td> <td>416/293 325/538</td> <td>2.37 (1.14, 3.59) 2.05 (1.36, 2.75)</td> <td>88% 81%</td> <td>&lt;0.01 &lt;0.01</td> <td>0.19</td>	Serum PTH	1. Asian Europe	3 7	416/293 325/538	2.37 (1.14, 3.59) 2.05 (1.36, 2.75)	88% 81%	<0.01 <0.01	0.19
C1A         2         260/137         2.74 (104, 4.43)         7%         0.07           BIA         3         99/109         202 (1.12, 22, 4.34)         -         -           Serum 25-0ED         I. Akin         3         166 (234, 21)         7%         0.02         0.25           Europe         4         207 (132, 24, 43)         8%         0.01         0.25           ECIA         1         166 (156         2.07 (232, 666)         -         -         -         2.75           ECIA         2         201017         -2.81 (329, 327)         5%         0.02         0.26           For transmot Net For Tr		2. ECLIA ELISA	3 1	282/448 42/63	2.20 (1.46, 2.94) 0.80 (0.32, 1.28)	55% -	0.11	18.9
MX         I         38/4         2.50 (1.3.4, 2.4)         ·         ·         ·           Seum 25-OHD         I. Akian         3         416(233)         -0.16 (6.4.3, 4.2.1)         76%         0.02         0.05           EGLA         2         260137         -2.81 (-2.9.3, 6.6)         -         -         2.75           EGLA         2         260137         -2.81 (-2.9.3, 6.6)         -         -         2.75           Effore treatment vs. /fer: treatment PA         2         378/378         -0.00 (-0.19, 0.01)         96%         -0.01         0.56           Europe*         7         264/224         -0.06 (-0.09, 0.04)         0.6%         -         -         5.16           Serum PTH         Akian         2         214731         2.28 (-0.8, 6.8)         91%         -0.01         0.01           Europe*         10         351/341         2.28 (0.60, 5.77)         91%         -0.01         0.01           Europe*         10         351/341         2.85 (1.40, 2.54)         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -         -		CLIA RIA	2 3	260/137 99/109	2.74 (1.04, 4.43) 2.02 (1.12, 2.92)	70% 71%	0.07 0.03	
Lunope         *         LorAsy         11.10 (30.05, 84.3)         05%         0.00           2. ECLIA         1         156/156         207 (2.52, 666)         -         -         2.75           CIA         2         260/137         -2.81 (9.29, 3.67)         89%         0.02           Bfore treatment vs. Jber-treatment VA         -         3.85/178         -0.09 (0.09, 0.01)         0%         0.05           Serum calcium         Asian         1         9999         2.57 (1.96, 5.18)         -         -         5.16           CiAa         1         9999         2.57 (1.96, 5.18)         -         -         5.16           Europe         10         311/41         2.89 (0.89, 6.68)         91%         0.01         0.01           Europe         10         311/41         2.83 (1.60, 1.57)         91%         0.01         0.01           Europe         10         311/41         2.83 (1.60, 1.57)         91%         0.01         0.01           Europe         1         44/14         3.33 (1.75, 7.14)         7.83         -         -         -         -         -         -         -         -         -         -         -         -         - <t< td=""><td>Serum 25-OHD</td><td>1. Asian</td><td>1 3</td><td>58/74 416/293 257/439</td><td>-0.16 (-6.34, 4.21)</td><td>- 76%</td><td>0.02</td><td>0.95</td></t<>	Serum 25-OHD	1. Asian	1 3	58/74 416/293 257/439	-0.16 (-6.34, 4.21)	- 76%	0.02	0.95
CLA         2         2001/3         -2.2.1 (-3.2.) (-3.2.) (-3.7.) (-3.7.)         0.1.2           CLA         4         207(4.3)         11.15 (-3.0.2), 8.43         9.89         0.1.2           Bfor-treatment v. Aft		2. ECLIA	4	156/156	-11.13(-30.75, 8.45) 2.07 (-2.52, 6.66)		- 0.12	2.75
Begine Produment V3.         Unitered and interval i		CLA CLA	4	257/439	-2.81 (-9.29, 3.67) -11.15 (-30.75, 8.45)	59% 89%	<0.12	
Serum calcium         Asian         2         378/378         -0.09 (0.19, 0.01)         92%         <0.01         0.25           Lurope*         7         244/244         -0.06 (-0.09, -0.04)         0%         0.56           Urine calcium         Asian         1         99/99         2.57 (1.96, 3.18)         -         -         5.16           Europe*         6         225/225         1.46 (0.71, 2.20)         36%         0.01         0.01           Europe         10         351/341         2.58 (1.60, 3.57)         9.1%         <0.01	Before-treatment vs.	After-treatment PA						
Urine calcium         Asian         1         9999         2.57 (1.95, 318)         -         -         -         5           Serum PTH         1. Asian         2         114/114         2.89 (4.0, 2.20)         36%         0.01         0.01           Europe         10         351/341         2.58 (1.60, 3.57)         91%         <0.01	Serum calcium	Asian Europe*	2 7	378/378 264/264	-0.09 (-0.19, 0.01) -0.06 (-0.09, -0.04)	92% 0%	<0.01 0.56	0.26
Serum PTH         1. Asian         2         114/114         2.89 (6.80, 6.58)         91%         <0.01           Larope         10         351/341         2.58 (1.69, 6.58)         91%         <0.01	Urine calcium	Asian Europe*	1 6	99/99 225/225	2.57 (1.96, 3.18) 1.46 (0.71, 2.20)	- 36%	0.17	5.16
22CLLA*4173/1732.05 (1.42, 2.8)0%0.9797.87CLA136/360.62 (-0.30, 1.54)CLA4154/1543.83 (2.22, 5.44)75%0.001LISA142/320.68 (0.10, 1.26)Mix142/320.68 (0.10, 2.6)RIA114/143.23 (1.75, 4.71)Serum 25-OHD1Asian274/74-1.21 (6.70.01, 5.68)95%0.001Europe'7286/286-3.51 (-7.51, 0.49)0%0.81CLA*5192/192-3.60 (-9.64, 2.44)0%0.81ECLA159/59-2.1.30 (2.72, -1.53, 0)ECLA159/59-2.1.30 (2.72, -1.53, 0)Tottered vs. Bilderr/ FV115/15-0.04 (-0.04, 0.001)0%0.64ECLA159/59-2.1.30 (2.72, -1.53, 0)ECLA159/59-2.1.30 (2.72, -1.53, 0)Without ACTH638/453-0.01 (-0.01, 0.01)0%0.64Unrope3151/105-0.04 (-0.04, 0.001)3%0.191.11Urine alcum #Asian*638/453-0.02 (-0.04, 0.00)3%0.01-Urine alcum #Asian*638/4530.90 (-0.37, 0.51)0%0.640.01Urine alcum #Asian*638/4530.90 (-0.03, 0.11)<	Serum PTH	1. Asian Europe	2 10	114/114 351/341	2.89 (-0.89, 6.68) 2.58 (1.60, 3.57)	91% 91%	<0.01 <0.01	0.01
CLIA         4         154/154         3.33         75%         <0.01           ELISA         1         42/32         0.68<(0.10, 1.26)		2. ECLIA* CLA	4 1	173/173 36/36	2.05 (1.42, 2.68) 0.62 (-0.30, 1.54)	0%	0.97	37.87
ELISA         1         42/32         0.68 (0.10, 1.26)         -         -           NIX         1         46/46         4.09 (25, 5.64)         -         -           RIA         1         14/14         3.23 (175, 4.71)         -         -           Serum 25-OHD         1. Asian         2         74/74         -12.16 (-30.01, 5.68)         95%         <0.01		CLIA	4	154/154	3.83 (2.22, 5.44)	75%	< 0.01	
International Serum 25-OHDI. AsianI.I. MarkDescriptionOptimizationSerum 25-OHD1. Asian274/74 $-12.16$ (3.001, 5.68)95% $<0.01$ 0.86Europe*7286/286 $-3.51$ ( $-7.51$ , $0.49$ )0%0.950.862. ELISA163/63 $-3.24$ ( $9.45$ , $2.97$ )26.77CLA*5192/192 $-3.60$ ( $9.66$ , $2.44$ )0%0.81ECLIA115/15 $-3.00$ ( $8.65$ , $2.47$ )RIA113/11 $-4.00$ ( $-1.45$ , $6.45$ )Unilateral vs. Bilateral vs.Bilateral vs.Bilateral vs.Serum calcium #1. Asian*6338/453-0.01 ( $-0.01$ , $0.01$ )0%0.643.38Colspan="4">Colspan=		ELISA Mix RIA	1 1	42/32 46/46	$\begin{array}{c} 0.68 \ (0.10, \ 1.26) \\ 4.09 \ (2.54, \ 5.64) \\ 3.23 \ (1.75, \ 4.71) \end{array}$	-	-	
Seturn 25-OTD         I. Asant         2         74/74         1-1210 (-3001, 308)         95/8         6001         030           Europe*         7         286/286         -3.511 (-5.51, 0.49)         0%         0.95           2. ELISA         1         63/63         -3.24 (-9.45, 2.97)         -         -         26.77           CLA*         5         192/192         -3.60 (-9.64, 2.44)         0%         0.81           ECLIA         1         15/15         -3.09 (-8.65, 2.47)         -         -           RIA         1         31/31         -4.00 (-14.45, 6.45)         -         -           Wilhactent vs. Bilateral vs.         Bilateral         P         -         -         -           Serum calcium #         1. Asian*         6         338/453         -0.01 (-0.01, 0.01)         0%         0.64           Without ACTH         4         149/255         -0.02 (-0.04, 0.00)         36%         0.19         1.11           Without ACTH         2         199/199         0.09 (-0.37, 0.54)         0%         0.47         0           Europe         2         151/105         0.81 (-0.50, 2.12)         85%         -0.01           Urine calcium         Asian*	Somum 25 OHD	1 Acien	2	74/74	12.16 ( 20.01 .5.69)	05%	<0.01	0.96
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Serum 25-OTID	Europe*	7	286/286	-3.51 (-7.51, 0.49)	93% 0%	0.95	0.00
ECIA         3         152/152         -3.00 (5.05, 2.47)         0.%         0.81           ECIA         1         59/59         -21.30 (-27.27, -15.33)         -         -           RIA         1         31/31         -400 (-14.45, 6.45)         -         -           Unilateral vs. Bilateral VA           Serum calcium #         1. Asian*         6         338/453         -0.01 (-0.01, 0.01)         0%         0.64         3.38           2. With ACTH         3         151/105         -0.04 (-0.06, -0.01)         44%         0.17         1.11           Without ACTH         5         340/303         -0.01 (-0.03, 0.01)         11%         0.34         1.11           Urine calcium         Asia*         2         199/199         0.09 (-0.37, 0.54)         0%         0.47         0           Europe         2         81/81         0.06 (-2.66, 2.78)         85%         <0.01		2. ELISA	1	63/63	-3.24 (-9.45, 2.97)	-	-	26.77
RIA         1         31/31         -4.00 (-14.8, 6.45)         -           Unilateral vs. Bilateral Vs.         Serum calcium #         1. Asian*         6         338/453         -0.01 (-0.01, 0.01)         0%         0.64         3.38           Serum calcium #         1. Asian*         6         338/453         -0.04 (-0.06, -0.01)         44%         0.17           2. With ACTH         4         149/255         -0.02 (-0.04, 0.00)         36%         0.19         1.11           Urine calcium         Asian*         2         199/199         0.09 (-0.37, 0.54)         0%         0.47         0           Urine calcium         Asian*         2         199/199         0.09 (-0.37, 0.54)         0%         0.47         0           Serum PTH         1. Asian*         6         338/453         0.99 (0.46, 1.51)         29%         0.22         0.02           Serum PTH         1. Asian*         6         338/453         0.99 (0.46, 1.51)         29%         0.02         0.01           Serum PTH         1. Asian*         5         262/370         0.81 (-0.50, 2.12)         83%         <0.01           3. ECLIA*         5         262/370         0.87 (0.34, 1.40)         28%         0.23         5.94 </td <td></td> <td>ECLIA ECLA</td> <td>1</td> <td>15/15</td> <td>-3.09 (-8.65, 2.47) -21.30 (-27.27, -15.33)</td> <td></td> <td>-</td> <td></td>		ECLIA ECLA	1	15/15	-3.09 (-8.65, 2.47) -21.30 (-27.27, -15.33)		-	
Multicaral vs. Bilateral PA         Serum calcium #       1. Asian*       6       338/453       -0.01 (-0.01, 0.01)       0%       0.64       3.38         Europe       3       151/105       -0.04 (-0.06, -0.01)       44%       0.17       1.11         2. With ACTH       4       149/255       -0.02 (-0.04, 0.00)       36%       0.19       1.11         Without ACTH       5       340/303       -0.01 (-0.03, 0.01)       11%       0.34         Urine calcium       Asian*       2       199/199       0.09 (-0.37, 0.54)       0%       0.47       0         Europe       2       81/81       0.06 (-2.66, 2.78)       85%       <0.01		RIA	1	31/31	-4.00 (-14.45, 6.45)	-	-	
Serum calcium #       1. Asian*       6       338/453       -0.01 (-0.01, 0.01)       0%       0.64       3.38         Europe       3       151/105       -0.04 (-0.06, -0.01)       44%       0.17         2. With ACTH       4       149/255       -0.02 (-0.04, 0.00)       36%       0.19       1.11         Without ACTH       5       340/303       -0.01 (-0.03, 0.01)       11%       0.34         Urine calcium       Asian*       2       199/199       0.09 (-0.37, 0.54)       0%       0.47       0         Europe       2       81/81       0.06 (-2.66, 2.78)       85%       <0.01	Unilateral vs. Bilate	ral PA			· · · /			
2. With ACTH       4       149/255       -0.02 (-0.04, 0.00)       36%       0.19       1.11         Without ACTH       5       340/303       -0.01 (-0.03, 0.01)       11%       0.34         Urine calcium       Asian*       2       199/199       0.09 (-0.37, 0.54)       0%       0.47       0         Europe       2       81/81       0.06 (-2.66, 2.78)       85%       <0.01	Serum calcium #	1. Asian* Europe	6 3	338/453 151/105	-0.01 (-0.01, 0.01) -0.04 (-0.06, -0.01)	0% 44%	0.64 0.17	3.38
Urine calcium         Asian*         2         199/199         0.09 (-0.37, 0.54)         0%         0.47         0           Europe         2         81/81         0.06 (-2.66, 2.78)         85%         <0.01		2. With ACTH Without ACTH	4 5	149/255 340/303	-0.02 (-0.04, 0.00) -0.01 (-0.03, 0.01)	36% 11%	0.19 0.34	1.11
Serum 25-OHD #         1. Asian*         6         338/453         0.99 (0.46, 1.51)         29%         0.22         0.02           2. With ACTH*         4         149/255         1.12 (-0.90, 3.14)         0%         0.68         0.19           2. With ACTH*         4         149/255         1.12 (-0.90, 3.14)         0%         0.68         0.19           3. ECLIA*         5         262/370         0.87 (0.34, 1.40)         28%         0.23         5.94           RIA         2         58/57         0.32 (-1.47, 2.11)         73%         0.05         7           Mix         1         123/119         1.52 (0.56, 2.48)         -         -         -           Mix         1         46/12         3.34 (1.08, 5.60)         -         -         -           Serum 25-OHD #         1. Asian*         3         222/218         -4.45 (-7.58, -1.33)         0%         0.98         0.14           Europe*         3         151/105         -6.10 (-14.03, 1.82)         3%         0.35         0.07           Without ACTH*         2         93/74         -5.55 (-12.81,1.70)         0%         0.58         0.07	Urine calcium	Asian* Europe	2	199/199 81/81	0.09 (-0.37, 0.54)	0% 85%	0.47	0
2. With ACTH*       4       149/255       1.12 (-0.90, 3.14)       0%       0.68       0.19         Without ACTH       5       340/303       1.09 (-0.01, 2.19)       78%       <0.01	Serum PTH	1. Asian* Europe	6	338/453	0.99 (0.46, 1.51)	29% 83%	0.22	0.02
3. ECLIA*       5       262/370       0.87 (0.34, 1.40)       28%       0.23       5.94         RIA       2       58/57       0.32 (-1.47, 2.11)       73%       0.05         CLIA       1       123/119       1.52 (0.56, 2.48)       -       -         Mix       1       46/12       3.34 (1.08, 5.60)       -       -         Serum 25-OHD #       1. Asian*       3       222/218       -4.45 (-7.58, -1.33)       0%       0.98       0.14         Europe*       3       151/105       -6.10 (-14.03, 1.82)       3%       0.35       0.07         Without ACTH*       2       93/74       -5.55 (-12.81,1.70)       0%       0.58       0.07		2. With ACTH* Without ACTH	4	149/255	1.12 (-0.90, 3.14) 1.09 (-0.01, 2.19)	0% 78%	0.68	0.19
KIN     Z     5057     6.32 (*1.4, 2.11)     75.0     6.03       CLIA     1     123/119     1.52 (0.56, 2.48)     -     -       Mix     1     46/12     3.34 (1.08, 5.60)     -     -       Serum 25-OHD #     1. Asian*     3     222/218     -4.45 (-7.58, -1.33)     0%     0.98     0.14       Europe*     3     151/105     -6.10 (-14.03, 1.82)     3%     0.35     0.07       Vithout ACTH*     2     93/74     -5.55 (-12.81,1.70)     0%     0.58     0.07		3. ECLIA*	5	262/370	0.87 (0.34, 1.40) 0.32 (-1.47, 2.11)	28% 73%	0.23	5.94
Serum 25-OHD #         1. Asian*         3         222/218         -4.45 (-7.58, -1.33)         0%         0.98         0.14           Europe*         3         151/105         -6.10 (-14.03, 1.82)         3%         0.35         0.07           2. With ACTH*         2         93/74         -5.55 (-12.81,1.70)         0%         0.58         0.07           Without ACTH*         4         280/249         -4.51 (-7.68, -1.34)         0%         0.60		CLIA Mix	1	123/119 46/12	1.52 (0.56, 2.48) 3.34 (1.08, 5.60)	-	-	
2. With ACTH*     2     93/74     -5.55 (-12.81,1.70)     0%     0.58     0.07       Without ACTH*     4     280/249     -4.51 (-7.68,-1.34)     0%     0.60	Serum 25-OHD #	1. Asian* Europe*	3 3	222/218 151/105	-4.45 (-7.58, -1.33) -6.10 (-14.03, 1.82)	0% 3%	0.98 0.35	0.14
		2. With ACTH* Without ACTH*	2 4	93/74 280/249	-5.55 (-12.81,1.70) -4.51 (-7.68,-1.34)	0% 0%	0.58 0.60	0.07

TABLE 3 Subgroup analyses of study location, the assay used to measure serum PTH and 25-OHD, and the AVS procedure.

(Continued)

Item	Subgroup	N of studies	N of patients	MD (95% CI)	$I^2$	P-value for I <sup>2</sup>	$\mathbf{X}^2$
	3. ECLIA	1	76/80	-4.91 (-11.45, 1.63)	-	-	0.18
	CLA*	3	151/105	-6.10 (-14.03, 1.82)	3%	0.35	
	ECLA	1	123/119	-3.75 (-13.39, 5.89)	-	-	
	Unknown	1	23/19	04.41 (-8.23, -0.59)	-	-	

TABLE 3 Continued

N, number; MD, mean difference; 95% CI, 95% Confidence Intervals; CLA, chemiluminescence assay; ECLA, electro-chemiluminescence assay; ECLA, electro-chemiluminescence immunoassay; ELISA, enzyme linked immunosorbent assay; CLIA, chemiluminescent immunoassay; RIA, immunoradiometric assays; \*I<sup>2</sup><50% in subgroup analysis; # I<sup>2</sup><50% before subgroup analysis.

suggesting that vitamin D might be involved in the action of aldosterone in terms of bone metabolism. Vitamin D increases the intestinal absorption of calcium and phosphorus, re-absorption of calcium and phosphate in the renal tubules, and bone calcium deposition. Reduced levels of serum vitamin D stimulate PTH secretion and upregulate the RAAS system (44-48); the 1,25(OH)  $_2$ D receptor complex inhibits the expression of renin *in vitro* (43), (49), (50). In PA patients, the level of the vitamin D receptor (VDR) may be associated with that of a marker of osteoclast activation, thus tartrateresistant acid phosphatase 5b (TRACP-5b) (6). Fibroblast growth factor 23 (FGF23) is a phosphorylated protein regulated by phosphate and 1,25(OH)<sub>2</sub>D. The latter stimulates the production of FGF23 and creates a negative feedback loop that regulates the production itself (51), as well as PTH secretion. FGF23 plays roles in PA-related HPT and improved parathyroid function after adrenalectomy in PA patients (52), but vitamin D supplementation does not completely correct HPT in PA patients (31), (10). Low vitamin D levels may (together with high aldosterone levels) affect PTH secretion and bone metabolism in PA patients, increasing the OP risk.

## Risk of OP in PA patients

After excluding the effect of hypertension (23), PA patients still had a higher fracture risk than general populations (28), (13), (23), (22). Wu et al. (53) confirmed a high prevalence of such fractures in a prospective cohort study. The BMD is commonly used to evaluate bone strength. We found no significant difference in the BMD of either the lumbar spine or femoral neck before and after PA treatment. We did not meta-analyze the BMD data of works that compared PA and EH groups because there were few such studies. However, Petramala et al. (26) and Salcuni et al. (28) found that the osteopenia and OP rates in PA patients were significantly higher than in EH patients, healthy subjects, and those with adrenal nonfunctioning tumors (NFAs). This was confirmed by another study comparing patients with PA and secondary aldosteronism (9).

The trabecular bone score (TBS) is a new indicator of bone microstructure, used to evaluate bone quality and fracture risk. Several studies have suggested that aldosterone may trigger osteopenia by destroying bone microstructure rather than by reducing the BMD (5), (54); the TBS may be a better indicator than the BMD when screening for OP in PA patients. Although no significant BMD changes were evident in early-stage PA patients, bone turnover increased (as revealed by changes in the CTX and PINP levels) (18). Unfortunately, no study has used the TBS to compare EH and PA patients.

The effect of aldosterone on BMD remains controversial (28), (23), and the mechanism of that has not been fully elucidated. Furthermore, more research is needed on how aldosterone may affect bone metabolism and the possible association between TBS and aldosterone in the future.

# Does bone metabolism differ between unilateral and bilateral PA patients?

This possibility remains controversial (14), (17), (25), (26), (29), (15), (11, 13, 19), (55), (56). All except three studies that we reviewed found that the serum PTH levels differed between unilateral and bilateral PA patients; the exceptions were Kometani et al., Jiang et al., and Riester et al. (25), (11), (55). Petramala et al. (26) found that patients with aldosterone-producing adenomas (APAs) exhibited more bone remodeling than did those with idiopathic hyperaldosteronism (IHA). Yokomoto et al. (13) reported that unilateral PA was an independent risk factor for vertebral fracture. We found that, in patients with unilateral PA, the serum PTH level was higher and the serum 25-OHD level lower than in patients with bilateral PA, which meant that a high serum aldosterone level is associated with a high serum PTH level, indicating that unilateral PA patients are at higher risk of sHPT.

### Strengths and limitations

There were 2 meta-analyses before our research. Loh et al. (4) published a conference abstract in 2019, meta-analyzing the difference between PA (n=352) and non-PA (n=587) patients, and between before and after treatment in PA patients. Shi et al.

(3) just meta-analyzed the difference between PA and EH patients with 15 articles in 2020. Unlike previous work (3), (4), we are the first to review systematically and meta-analyze the possible effects of PA subtypes on bone metabolism. The number of included papers and the sample size of the present study are larger than those of the previous work. However, certain limitations of our work should be acknowledged. First, most included studies were observational and had small patient numbers. Second, the assays used to measure the levels of plasma aldosterone, and serum PTH and 25-OHD, varied. Third, some studies evidenced heterogeneity. Although the sensitivity analyses eliminated most heterogeneity, a possibility of bias remains. Fourth, few works dealt with the effects of different PA subtypes on BMD; we could engage in only descriptive analyses.

# Conclusion

Excess aldosterone was associated with decreased serum calcium, elevated urinary calcium, and elevated PTH levels; these effects may be enhanced by low serum 25-OHD levels. The risks of OP and fracture might be elevated in PA patients, especially unilateral PA patients, but could be reduced after medical treatment or adrenal surgery. The lack of BMD changes after treatment, indicates, however, that PTH and calcium changes may also represent an epiphenomenon of limited clinical significance, so more research is needed, either to confirm, or to refute the notion of any significant change in fracture rate in PA patients. TBS may be a better indicator than BMD when screening for OP in PA patients. More research is needed on how aldosterone may affect bone metabolism and the possible association between TBS and aldosterone.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## References

1. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int* (2007) 18(10):1319–28. doi: 10.1007/s00198-007-0394-0

2. Rizzoli R, Biver E. Glucocorticoid-induced osteoporosis: who to treat with what agent? *Nat Rev Rheumatol* (2015) 11(2):98-109. doi: 10.1038/nrrheum.2014.188

3. Shi S, Lu C, Tian H, Ren Y, Chen T. Primary aldosteronism and bone metabolism: A systematic review and meta-analysis. *Front Endocrinol (Lausanne)* (2020) 11:574151. doi: 10.3389/fendo.2020.574151

## Author contributions

AW and ZL designed the study. HL and XH collected the data. AW performed the meta-analysis and drafted the manuscript. JL, HX, ZN and LZ partially planned the research. ZL edited the manuscript. All authors contributed to the article and have approved the submitted version.

# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

# Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/ fendo.2022.1027841/full#supplementary-material

#### SUPPLEMENTARY FIGURE 1

Subgroup analysis of PA and EH (A: serum calcium, B: urine calcium, C: serum PTH, D: serum 25-OHD).

#### SUPPLEMENTARY FIGURE 2

Subgroup analysis of before-treatment and after-treatment PA patients (A: serum calcium, B: urine calcium, C: serum PTH, D: serum 25-OHD).

#### SUPPLEMENTARY FIGURE 3

Subgroup analysis of unilateral and bilateral PA patients (**A**: serum calcium, **B**: urine calcium, **C**: serum PTH, **D**: serum 25-OHD).

4. Loh HH, Yee A, Loh HS. Bone health among patients with primary aldosteronism: a systematic review and meta-analysis. *Minerva Endocrinol* (2019) 44(4):387-96. doi: 10.23736/S0391-1977.18.02867-5

5. Kim B-J, Lee SH, Koh J-M. Bone health in adrenal disorders. *Endocrinol Metab* (2018) 33(1):1-8. doi: 10.3803/EnM.2018.33.1.1

 Gao X, Yamazaki Y, Tezuka Y, Onodera Y, Ogata H, Omata K, et al. The crosstalk between aldosterone and calcium metabolism in primary aldosteronism: A possible calcium metabolism-associated aberrant 'neoplastic' steroidogenesis in adrenals. J Steroid Biochem Mol Biol (2019) 193:105434. doi: 10.1016/j.jsbmb.2019.105434 7. Brown JM, Vaidya A. Interactions between adrenal-regulatory and calciumregulatory hormones in human health. *Curr Opin Endocrinol Diabetes Obes* (2014) 21(3):193–201. doi: 10.1097/MED.000000000000062

8. Zavatta G, Di Dalmazi G, Altieri P, Pelusi C, Golfieri R, Mosconi C, et al. Association between aldosterone and parathyroid hormone levels in patients with adrenocortical tumors. *Endocr Pract* (2022) 28(1):90–5. doi: 10.1016/j.eprac.2021.09.002

9. Tang W, Chai Y, Jia H, Wang B, Liu T, Wang H, et al. Different roles of the RAAS affect bone metabolism in patients with primary aldosteronism, gitelman syndrome and bartter syndrome. *BMC Endocr Disord* (2022) 22(1) : 38. doi: 10.1186/s12902-022-00955-2

10. Liu Y, Yang G, Pei Y, Dou J, Lyu Z, Du J, et al. Value of serum parathyroid hormone in the diagnosis of primary aldosteronism. *Nat Med J China* (2021) 101 (34):2674–80. doi: 10.3760/cma.j.cn112137-20210111-00088

11. Kometani M, Yoneda T, Aono D, Gondoh-Noda Y, Matsuoka T, Higashitani T, et al. Primary aldosteronism with parathyroid hormone elevation: A single-center retrospective study. *Intern Med* (2021) 60(7):993–8. doi: 10.2169/internalmedicine.5282-20

12. Gravvanis C, Papanastasiou L, Glycofridi S, Voulgaris N, Tyfoxylou E, Theodora K, et al. Hyperparathyroidism in patients with overt and mild primary aldosteronism. *Hormones (Athens)* (2021) 20(4):793–802. doi: 10.1007/s42000-021-00319-w

13. Yokomoto-Umakoshi M, Sakamoto R, Umakoshi H, Matsuda Y, Nagata H, Fukumoto T, et al. Unilateral primary aldosteronism as an independent risk factor for vertebral fracture. *Clin Endocrinol* (2020) 92(3):206–13. doi: 10.1111/cen.14145

14. Tuersun T, Luo Q, Zhang Z, Wang G, Zhang D, Wang M, et al. Abdominal aortic calcification is more severe in unilateral primary aldosteronism patients and is associated with elevated aldosterone and parathyroid hormone levels. *Hypertens Res* (2020) 43(12):1413–20. doi: 10.1038/s41440-020-0529-7

15. Asbach E, Bekeran M, König A, Lang K, Hanslik G, Treitl M, et al. Primary and secondary hyperparathyroidism in patients with primary aldosteronism - findings from the German conn's registry. *Exp Clin Endocrinol Diabetes* (2020) 128 (4):246–54. doi: 10.1055/a-1027-6472

16. Adolf C, Braun LT, Fuss CT, Hahner S, Künzel H, Handgriff L, et al. Spironolactone reduces biochemical markers of bone turnover in postmenopausal women with primary aldosteronism. *Endocrine* (2020) 69(3):625–33. doi: 10.1007/s12020-020-02348-8

17. Lenzini L, Prisco S, Vanderriele PE, Lerco S, Torresan F, Maiolino G, et al. PTH modulation by aldosterone and angiotensin II is blunted in hyperaldosteronism and rescued by adrenalectomy. *J Clin Endocrinol Metab* (2019) 104(9):3726-34. doi: 10.1210/jc.2019-00143

18. Loh HH, Kamaruddin NA, Zakaria R, Sukor N. Improvement of bone turnover markers and bone mineral density following treatment of primary aldosteronism. *Minerva Endocrinol* (2018) 43(2):117-25. doi: 10.23736/S0391-1977.16.02553-0

19. Lim JS, Hong N, Park Park S, Park S II, Oh YT, Yu MH, et al. Effects of altered calcium metabolism on cardiac parameters in primary aldosteronism. *Endocrinol Metab* (2018) 33(4):485–92. doi: 10.3803/EnM.2018.33.4.485

20. Shu X, Mei M, Ma L, Wang Z, Yang S, Hu J, et al. Postmenopausal osteoporosis is associated with elevated aldosterone/renin ratio. *J Hum Hypertens* (2018) 32(7):524–30. doi: 10.1038/s41371-018-0069-7

21. Wu V-C, Chang C-H, Wang C-Y, Lin Y-H, Kao T-W, Lin P-C, et al. Risk of fracture in primary aldosteronism: A population-based cohort study. *J Bone Miner Res* (2017) 32(4):743–52. doi: 10.1002/jbmr.3033

22. Salcuni AS, Carnevale V, Battista C, Palmieri S, Eller-Vainicher C, Guarnieri V, et al. Primary aldosteronism as a cause of secondary osteoporosis. *Eur J Endocrinol* (2017) 177(5):431–7. doi: 10.1530/EJE-17-0417

23. Notsu M, Yamauchi M, Yamamoto M, Nawata K, Sugimoto T. Primary aldosteronism as a risk factor for vertebral fracture. *J Clin Endocrinol Metab* (2017) 102(4):1237–43. doi: 10.1210/jc.2016-3206

24. Zhang L-X, Gu W-J, Li Y-J, Wang Y, Wang W-B, Wang A-P, et al. PTH is a promising auxiliary index for the clinical diagnosis of aldosterone-producing adenoma. *Am J Hypertens* (2016) 29(5):575–81. doi: 10.1093/ajh/hpv146

25. Jiang Y, Zhang C, Ye L, Su T, Zhou W, Jiang L, et al. Factors affecting parathyroid hormone levels in different types of primary aldosteronism. *Clin Endocrinol (Oxf)* (2016) 85(2):267-74. doi: 10.1111/cen.12981

26. Petramala L, Zinnamosca L, Settevendemmie A, Marinelli C, Nardi M, Concistrè A, et al. Bone and mineral metabolism in patients with primary aldosteronism. *Intl J Endocrinol* (2014) 2014:6. doi: 10.1155/2014/836529

27. Ceccoli L, Ronconi V, Giovannini L, Marcheggiani M, Turchi M, Boscaro G, et al. Bone health and aldosterone excess. *Osteoporos Int* (2013) 24(11):2801–7. doi: 10.1007/s00198-013-2399-1

28. Salcuni AS, Palmieri S, Carnevale V, Morelli V, Battista C, Guarnieri V, et al. Bone involvement in aldosteronism. *J Bone Miner Res* (2012) 27(10):2217–22. doi: 10.1002/jbmr.1660 29. Rossi GP, Ragazzo F, Seccia TM, Maniero C, Barisa M, Calò LA, et al. Hyperparathyroidism can be useful in the identification of primary aldosteronism due to aldosterone-producing adenoma. *Hypertension* (2012) 60(2):431–6. doi: 10.1161/HYPERTENSIONAHA.112.195891

30. Pilz S, Kienreich K, Drechsler C, Ritz E, Fahrleitner-Pammer A, Gaksch M, et al. Hyperparathyroidism in patients with primary aldosteronism: cross-sectional and interventional data from the GECOH study. *J Clin Endocrinol Metab* (2012) 97 (1):E75–79. doi: 10.1210/jc.2011-2183

31. Maniero C, Fassinab A, Secciaa TM, Toniatod A, Iacobonee M, Plebanic M, et al. Mild hyperparathyroidism: a novel surgically correctable feature of primary aldosteronism. *J Hypertens* (2012) 30(2):390–5. doi: 10.1097/HJH.0b013e32834f0451

32. Rossi E, Perazzoli F, Negro A, Sani C, Davoli S, Dotti C, et al. Acute effects of intravenous sodium chloride load on calcium metabolism and on parathyroid function in patients with primary aldosteronism compared with subjects with essential hypertension. *Am J Hypertens* (1998) 11(1 Pt 1):8–13. doi: 10.1016/s0895-7061(97)00366-x

33. Rossi E, Sani C, Perazzoli F, Casoli MC, Negro A, Dotti C. Alterations of calcium metabolism and of parathyroid function in primary aldosteronism, and their reversal by spironolactone or by surgical removal of aldosterone-producing adenomas. *Am J Hypertens* (1995) 8(9):884–93. doi: 10.1016/0895-7061(95)00182-O

34. Resnick LM, Laragh JH. Calcium metabolism and parathyroid function in primary aldosteronism. *Am J Med* (1985) 78(3):385–90. doi: 10.1016/0002-9343 (85)90328-6

35. Atashi F, Modarressi A, Pepper MS. The role of reactive oxygen species in mesenchymal stem cell adipogenic and osteogenic differentiation: a review. *Stem Cells Dev* (2015) 24(10):1150–63. doi: 10.1089/scd.2014.0484

36. Cauley JA, Danielson ME, Boudreau RM, Forrest KYZ, Zmuda JM, Pahor M, et al. Inflammatory markers and incident fracture risk in older men and women: the health aging and body composition study. *J Bone Miner Res* (2007) 22(7):1088–95. doi: 10.1359/jbmr.070409

37. Stehr CB, Mellado R, Ocaranza MP, Carvajal CA, Mosso L, Becerra E, et al. Increased levels of oxidative stress, subclinical inflammation, and myocardial fibrosis markers in primary aldosteronism patients. *J Hypertens* (2010) 28 (10):2120–6. doi: 10.1097/HJH.0b013e32833d0177

38. Carbone LD, Cross JD, Raza SH, Bush AJ, Sepanski RJ, Dhawan S, et al. Fracture risk in men with congestive heart failure risk reduction with spironolactone. *J Am Coll Cardiol* (2008) 52(2):135–8. doi: 10.1016/j.jacc.2008.03.039

39. Beavan S, Horner A, Bord S, Ireland D, Compston J. Colocalization of glucocorticoid and mineralocorticoid receptors in human bone. J Bone Miner Res (2001) 16(8):1496–504. doi: 10.1359/jbmr.2001.16.8.1496

40. Gupta M, Cheung CL, Hsu YH, Demissie S, L, Cupples A, Douglas PK, et al, et al. Identification of homogeneous genetic architecture of multiple genetically correlated traits by block clustering of genome-wide associations. *J Bone Miner Res* (2011) 26(6):1261–71. doi: 10.1002/jbmr.333

41. Brown J, Williams JS, Luther JM, Garg R, Garza AE, Pojoga LH, et al. Human interventions to characterize novel relationships between the reninangiotensin-aldosterone system and parathyroid hormone. *Hypertension (dallas tex. : 1979)* (2014) 63(2):273–80. doi: 10.1161/HYPERTENSIONAHA.113.01910

42. Ismail NA, Kamaruddin NA, Azhar Shah S, Sukor N. The effect of vitamin d treatment on clinical and biochemical outcomes of primary aldosteronism. *Clin Endocrinol (Oxf)* (2020) 92(6):509–17. doi: 10.1111/cen.14177

43. Forman JP, Williams JS, Fisher NDL. Plasma 25-hydroxyvitamin d and regulation of the renin-angiotensin system in humans. *Hypertension* (2010) 55 (5):1283–8. doi: 10.1161/HYPERTENSIONAHA.109.148619

44. Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, et al. Independent association between 1,25-dihydroxyvitamin d, 25-hydroxyvitamin d and the renin-angiotensin system: The ludwigshafen risk and cardiovascular health (LURIC) study. *Clin Chim Acta* (2010) 411(17–18):1354–60. doi: 10.1016/ j.cca.2010.05.037

45. Li YC, Kong J, Wei M, Chen Z-F, Liu SQ, Cao L-P. 1,25-dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* (2002) 110(2):229–38. doi: 10.1172/JCI15219

46. Vaidya A, Forman JP, Hopkins PN, Seely EW, Williams JS. 25hydroxyvitamin d is associated with plasma renin activity and the pressor response to dietary sodium intake in caucasians. *J Renin Angiotensin Aldosterone Syst* (2011) 12(3):311–9. doi: 10.1177/1470320310391922

 Vaidya A, Sun B, Larson C, Forman JP, Williams JS. Vitamin D3 therapy corrects the tissue sensitivity to angiotensin ii akin to the action of a converting enzyme inhibitor in obese hypertensives: an interventional study. J Clin Endocrinol Metab (2012) 97(7):2456–65. doi: 10.1210/jc.2012-1156

48. Matrozova J, Steichen O, Amar L, Zacharieva S, Jeunemaitre X, Plouin P-F. Fasting plasma glucose and serum lipids in patients with primary aldosteronism: a controlled cross-sectional study. *Hypertension* (2009) 53(4):605–10. doi: 10.1161/HYPERTENSIONAHA.108.122002

49. Grubler MR, Gaksch M, Kienreich K, Verheyen N, Schmid J, Hartaigh BWJO, et al. Effects of vitamin d supplementation on plasma aldosterone and renin-a randomized placebo-controlled trial. *J Clin Hypertens (Greenwich)* (2016) 18(7):608–13. doi: 10.1111/jch.12825

50. Yuan W, Pan W, Kong J, Zheng W, Szeto FL, Wong KE, et al. 1,25dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. *J Biol Chem* (2007) 282(41):29821–30. doi: 10.1074/jbc.M705495200

51. Kurpas A, Supeł K, Idzikowska K, Zielińska M. FGF23: A review of its role in mineral metabolism and renal and cardiovascular disease. *Dis Markers* (2021) 2021:8821292. doi: 10.1155/2021/8821292

52. Ragazzo F, Maniero C, Seccia TM, De Toni R, Rossi GP. The phosphatonin FGF23 is associated with the subtle hyperparathyroidism of patients with primary aldosteronism due to an aldosterone-producing adenoma. *High Blood Press Cardiovasc Prev* (2012) 19(3):168. doi: 10.2165/11632200-000000000-00000

53. Wu X, Yu J, Tian H. Cardiovascular risk in primary aldosteronism: A systematic review and meta-analysis. *Med (Baltimore)* (2019) 98(26):e15985. doi: 10.1097/MD.000000000015985

54. Harvey NC, Glüer CC, Binkley N, McCloskey EV, Brandi M-L, Cooper C., et al. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. *Bone* (2015) 78:216–24. doi: 10.1016/j.bone.2015.05.016

55. Riester A, Fischer E, Degenhart C, Reiser MF, Bidlingmaier M, Beuschlein F, et al. Age below 40 or a recently proposed clinical prediction score cannot bypass adrenal venous sampling in primary aldosteronism. *J Clin Endocrinol Metab* (2014) 99(6):E1035–1039. doi: 10.1210/jc.2013-3789

56. Rossi GP, Ragazzo F, Seccia TM, Maniero C, Barisa M, Calò LA, et al. Hyperparathyroidism can be useful in the identification of primary aldosteronism due to aldosterone-producing adenoma. *High Blood Press Cardiovasc Prev* (2012) 19(3):167. doi: 10.2165/11632200-000000000-00000