Bone Health in Children and Youth with Cystic Fibrosis: A Systematic Review and Meta-Analysis of Matched Cohort Studies

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Objective: To assess the evidence regarding the differences in areal bone mineral density (aBMD) between children and adolescents with cystic fibrosis (CF) compared with their healthy peers, based on data from longitudinal studies. Study design: We searched MEDLINE, SPORTDiscus, the Cochrane Library, PEDro (Physiotherapy Evidence Database), and Embase databases. Observational studies addressing the change of aBMD in children with CF and healthy children and adolescents were eligible. The DerSimonian and Laird method was used to compute pooled estimates of effect sizes (ES) and 95% CIs for the change of whole body (WB), lumbar spine (LS), and femoral neck (FN) aBMD. Results: Six studies with participants with CF and 26 studies with healthy participants were included in the systematic review and meta-analysis. For the analysis in children with CF, the pooled ES for the change of WB aBMD was 0.29 (95% CI –0.15 to 0.74), for the change of LS aBMD was 0.13 (95% CI –0.16 to 0.41), and for the change of FN aBMD was 0.09 (95% CI –0.39 to 0.57). For the analysis in healthy children, the pooled ES for the change of WB aBMD was 0.37 (95% CI 0.26-0.49), for the change of LS aBMD was 0.13 (95%CI –0.16 to 0.41), and for the change of FN aBMD was 0.52 (95% CI 0.19-0.85). Conclusions: aBMD development might not differ between children and adolescents with CF receiving medical care compared with their healthy peers. Further longitudinal studies in a CF population during growth and development are required to confirm our findings.

Introduction

Cystic fibrosis (CF) is an inherited disease affecting the correct functioning of numerous vital organs, such as the lungs and the gastrointestinal tract (1). It is caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene and it is the most prevalent (autosomal recessive) disorder in the Caucasian-race population. The median age at death, 29.1 years, has continuously increased over the last two decades, and nowadays more than half of the individuals with CF are 18 years or older (2), suggesting an increase in the likelihood of having long-term CF sequels. These include low areal bone mineral density (aBMD), osteoporosis-related fractures and abnormal excessive convex curvature of the spine (e.g. kyphosis) (3-5), which in turn may cause pain when breathing and impair physical activity levels, which can contribute to bone accrual (6). CF is also related to exocrine pancreatic insufficiency, characterised by a deficiency in the number of exocrine pancreatic enzymes and causing an inability to digest food and absorb nutrients, which affects proper development in children and adolescents with CF (1, 7). In this regard, a poor nutritional status has been associated with a reduction in lung function, impaired pulmonary muscle function, and tolerance levels towards exercise (8).

Multiple factors seem to explain the link between low aBMD and CF, including poor nutritional status, nutrient malabsorption and clinical status (9-12) but also a more direct pathway through the CFTR gene mutation, which may lower aBMD (11). The association between aBMD and CF may vary depending on whether it is looked at in growing or adult population. Findings from a systematic review and meta-analysis showed that 38% and 23.5% of the adults with CF had osteopenia and osteoporosis, respectively (13). It is

known that bone acquisition occurs throughout childhood and adolescence, with 80-90 % acquired by late adolescence, depending of the sites of the skeleton (14, 15). Therefore, the origins of bone disease in CF are likely to occur during childhood or adolescence.

The scientific evidence regarding bone mineralization in CF is controversial (4, 16-20). Some evidence points out the prevalence of low aBMD in children and adolescents (21-23), and suggest lung function and nutritional status as important determinants of low aBMD in CF (16, 23-25). The study of Reix, Bellon (26) showed that bone alterations may be already present in children younger than 6 years of age, and highlighted that monitoring bone status in this population is needed. In contrast, other studies highlight a minimal difference in bone mass in CF (relative to normal) but that this difference is more important at later life stages, such as adulthood (27-29). In this regard, the CF Foundation consensus statement on bone health and disease recommends monitoring CF adults with Dual energy X-ray Absorptiometry (DXA) and subsequent follow-up based on the findings (2).

DXA is considered the gold standard method for assessing aBMD and has been used worldwide not only in adults but also in children and adolescents (30). In a clinical setting, the most common sites measured with DXA are the lumbar spine, hip (total hip or proximal femur), and total body (31, 32). Considering the increase in life expectancy in people with CF and associated sequels, such as the increased risk of osteoporosis, examining whether low bone mass is already apparent in children and adolescents with CF must be viewed as a high priority. To the best of our knowledge, no meta-analysis has analysed whether aBMD differs between CF and healthy children and adolescents.

Therefore, this systematic review and meta-analysis aims to examine the differences in aBMD between children and adolescents with CF compared to their healthy peers based on data from longitudinal studies.

Methods

This study was reported according to the Meta-analysis of Observational Studies in Epidemiology statements (MOOSE) (33) and followed the recommendations of the Cochrane Collaboration Handbook (34). This systematic review and meta-analysis was registered through the International Prospective Register of Systematic Reviews (Registration number: CRD42018099671).

Search strategy

We systematically searched MEDLINE (via PubMed), SPORTDiscus, the Cochrane Library, PEDro (Physiotherapy Evidence Database) and Scopus (via databases from their inception until October, 2018). Observational studies addressing the change of aBMD in both, cystic fibrosis and healthy, across the childhood and adolescence period were eligible. The search strategy included the following terms for cystic fibrosis populations: (bone) AND (children OR adolescents OR young OR boys OR girls) AND ("cystic fibrosis"); and for healthy populations: (bone) AND (children OR adolescents OR young OR boys OR girls) AND (healthy). The literature search was complemented by reviewing citations of the articles considered eligible for the systematic review and authors were contacted to obtain missing information when necessary.

Study selection

The criteria for including studies were as follows: i) participants: cystic fibrosis population samples or healthy population samples; ii) study design: longitudinal studies, with prospective data collection; iii) exposure: bone development during the follow-up; and iv) outcome: aBMD. The criteria for excluding studies were as follows: i) reports not written in English or Spanish; ii) studies including individuals aged below 18 years old; and iii) non-eligible publication types, such as review articles, editorials, comments, guidelines or case-reports.

When more than one study provided data from the same sample, we only considered the one presenting the most detailed results or providing data for the largest sample size. However, data regarding sample characteristics could be extracted from multiple reports to obtain the most complete information

The literature search was independently conducted by two reviewers (EUG and LGM), and disagreements were solved by consensus or involving a third researcher (ICR).

Data extraction and quality assessment

The following data were extracted from the original reports (1) first author and year of publication, (2) country of the study where data were collected, (3) length of follow-up, (4) sample characteristics (age, sample size, BMI, stature, weight and type of population) and, (5) bone measurement characteristics (aBMD measurement method used, values for each aBMD [WB, LS and FN] at baseline and at end of follow-up).

Quality Assessment tool for Observational Cohort and Cross-sectional Studies from the National Heart, Lung and Blood Institute (35) was used to evaluate risk of bias for cohort and cross-sectional studies. Assessed methodological criteria included: research question,

population definition, participation rate, recruitment, sample size, analysis, timeframe, exposure levels, measures and assessment, outcome measures and blinding, loss at follow up and confounding variables. Each study was rated either as good (i.e., most criteria met, and with a low risk of bias), fair (i.e., some criteria met, with a moderate risk of bias), or poor (i.e., few criteria met, and with a high risk of bias).

Data extraction and quality assessment were independently performed by two researchers (EUG and LGM), and inconsistencies were solved by consensus or involving a third researcher (ICR).

Statistical analysis and data synthesis

The inverse-variance fixed effects method (36), were used to compute pooled estimates of effect size (ES) and respective 95% CI. When the studies presented aBMD mean values for baseline and end-point or aBMD mean value change, effect size (ES) were calculated. ES values around 0.2 were considered to be a weak effect, values around 0.5 were a moderate effect, values around 0.8 were a strong effect, and values larger than 1.0 were a very strong effect. In order to compare the differences in aBMD changes between cystic fibrosis and healthy population the meta-analysis was done separately. The heterogeneity of results across studies was assessed using the I^2 statistic (37). I^2 values are considered as: might not be important (0% to 40%), may represent moderate heterogeneity (30% to 60%), substantial heterogeneity (50% to 90%) or considerable heterogeneity (75% to 100%); the corresponding p-values were also taken into account (34).

Sensitivity analyses (systematic re-analysis while removing studies one at a time), and subgroup analyses were conducted in order to assess the robustness of the summary

estimates. Results of the sensitivity analyses were considered meaningful when the resulting estimates were modified beyond the confidence intervals of the original summary estimate. In addition, sensitivity analyses provided insight as to whether any particular study or subgroup accounted for a large proportion of heterogeneity among the correlation pooled estimations, based on the change in I^2 values (and associated categories previously reported).

Random-effects meta-regression analyses were performed to determine whether age and length of follow-up to examine their interaction effect on the aBMD change comparing healthy and cystic fibrosis populations. Finally, to assess publication bias, Egger's regression asymmetry test was used (38). A level of <0.10 was used to determine if publication bias might be present. Statistical analyses were performed using StataSE software, version 14 (StataCorp).

Results

Systematic Review

We identified 6 longitudinal studies (Table 1) (21, 39-43) about the development of aBMD in children and adolescents with cystic fibrosis. In parallel, we identified 29 studies (Table 2) (44-72) with longitudinal data of aBMD in healthy children and adolescents. The compilation of these studies allow us to compare the status of bone health in cystic fibrosis young with a healthy peers (control studies) over the time.

Regarding to the cystic fibrosis studies, these were carried out in 4 different countries: three from USA, one from Italy, one from New Zealand and one from Hungary. Reports were published between 1998 and 2017, and they included longitudinal studies using the

following designs: five were follow-up non-randomised studies and one was a randomised trial. Length of studies ranged from 9 months to 5 years.

All the participants suffered cystic fibrosis and one of the study the participants underwent liver transplantation. Included participants were aged between 4 and 18 years, with sample sizes ranging from 9 to 40 subjects. Concerning assessment methods carried out in the studies, all of them used a dual-energy x-ray absorptiometry scanner to measure bone outcomes: two studies used the model Hologic 1000W, one study used the model Hologic QDR 2000, two studies used the model Hologic QDR-4500, and one study used the model Lunar Prodigy.

Regarding to the control studies, these were realised in 12 different countries: one from Brazil, two from Spain, three from Switzerland, five from Australia, four from Canada, seven from USA, one from United Kingdom, one from Estonia, one from France, two from Sweden, one from Belgium and one from Denmark. Data were published between 1991 and 2017 and they included longitudinal studies using the following designs: twelve were follow-up non-randomised studies and seventeen were randomised-controlled trial. Length of studies ranged from 3 months to 14 years.

All the participants were healthy children and adolescents. The range age of the participants was 4 to 18 years, with sample sizes between 9 to 124. Concerning assessment methods carried out in the studies, all of them used a dual-energy x-ray absorptiometry scanner to measure bone outcomes: eight studies used the model Lunar Prodigy, one study used the model Hologic QDR 1500, three studies used the model Hologic QDR 2000, five studies used the model Hologic QDR 1000W, ten studies used

the model Hologic QDR 4500, one study used the model Hologic WB Delphi, and one study used the model Norland Medical XR800.

Study Quality

The risk of bias was evaluated by a quality assessment tool for observational cohort and cross-sectional studies for The National Institutes of Health (73). The cystic fibrosis studies showed a 33.3% of high risk of bias and 66.7% of moderate risk of bias. The control studies showed a 51.7 % of high risk of bias, a 44.8% of moderate risk of bias, and a 3.4% of low risk of bias.

When studies were analysed by individual domains, 100% of the cystic fibrosis studies defined a clearly research question, took into account the exposure(s) of interest measured prior to the outcome(s) being measured, the timeframe was sufficient, the exposure measures (independent and dependent variables) were clearly defined, valid, reliable, and implemented consistently, and presented a lower percentage of 20% of withdrawals/drop-outs. However, no study or just one had presented a sample size justification (power description, or variance and effect estimates) and had shortcomings in the blinding domain. On the other hand, approximately 100% of the control studies defined a clearly research question, the timeframe was sufficient, and the exposure measures (independent and dependent variables) were clearly defined, valid, reliable, and implemented consistently. However, less than 25% had presented a sample size justification (power description, or variance and effect estimates) and have shortcomings in the blinding domain.

(Electronic Supplementary Material Tables S2 and S3).

Meta-analysis

To more clearly display the pooled ES estimates of WB, LS, and FN aBMD, we have provided forest plots including the pooled ES estimates, their 95% CI and the I^2 heterogeneity statistic for healthy and cystic fibrosis children (Figures 2-4).

WB aBMD

Finally, for the analysis in cystic fibrosis children, the pooled ES for the change of WB aBMD was 0.29 (95% CI -0.15–0.74), with no heterogeneity (I^2 = 0.0%; p = 0.829). Furthermore, for the analysis in healthy children, the pooled ES for this change was 0.25 (95% CI 0.13–0.37), with not important heterogeneity (I^2 = 35.8%; p = 0.071) (Figure 2).

LS aBMD

Additionally, regarding the change of LS aBMD, the pooled ES in cystic fibrosis children was 0.13 (95% CI -0.16–0.41), with no heterogeneity (I^2 = 0.0%; p = 1.000). Besides in healthy children the pooled ES was 0.29 (95% CI 0.18–0.40), with not important heterogeneity (I^2 = 21.0%; p = 0.209) (Figure 3).

FN aBMD

For the analysis in cystic fibrosis children, the pooled ES for the change of FN aBMD was 0.09 (95% CI -0.39–0.57), with no heterogeneity (I^2 = 0.0%; p = 0.999). Furthermore, for the analysis in healthy children, the pooled ES for this change was 0.20 (95% CI 0.11–0.30), also with no heterogeneity (I^2 = 0.0%; p = 0.558) (Figure 4).

Sensitivity analysis, meta-regression subgroup analysis and publication bias

The pooled ES estimate was not significantly modified in magnitude or direction when individual study data were removed from the analysis one at a time.

The random-effects meta-regression model showed that length of follow up, age, BMI, height and weight were not related to FN, LS or WB aBMD change across studies either for cystic fibrosis children or for healthy children (Figures XXX-XXX in the Supplementary file).

Finally, evidence of publication bias was found by funnel plot asymmetry and Egger's test for the change of LS aBMD in cystic fibrosis children ($p = 0.027$) and for the change of WB aBMD in healthy children ($p = 0.073$) (Figures XXX-XXX in the Supplementary file).

Discussion

In the present systematic review and meta-analysis, children and adolescents affected by CF did not present lower aBMD compared with their peers without CF. To the best of our knowledge, this is the first meta-analysis analysing the status of aBMD in CF children and adolescents.

Among other factors, a poor nutritional status, nutrient malabsorption and clinical status have been suggested in previous investigations as determinants that may explain the association between low aBMD and CF (9-12). However, there is controversial in the scientific literature on whether CF patients present poorer bone mineralization (4, 16-20). Our data show that longitudinal changes in WB, LS and FN aBMD in children and adolescents with CF are not different from those found in their healthy peers. These

results are in accordance with the cross-sectional study by Buntain, Greer (10) in which it was found that well-nourished prepubertal children with CF had no significant differences in WB, LS and FN aBMD than a healthy control group. Young adults with CF have shown a low bone turnover with reduced bone formation but there is no evidence for increased bone resorption (74, 75). Nevertheless, it seems that the prevalence of CF-related bone disease increases with age (19, 76). For example, <5% of children with CF presented bone disease, increasing to 20% in adolescents and 55 to 65% in adults older than 45 years (29). Therefore, deficits in aBMD seem to be more evident in adulthood than childhood (10).

In contrast to our findings, previous investigations have shown bone disease in CF youth patients (16, 21-23, 26). Schulze, Cutchins (41) found that low bone mass was usual among their cohort of adolescent girls with CF, and approximately a 40% of the girls presented deficits in expected bone mineral content at the lumbar spine, and above 20% in expected bone mineral content at the WB. In this line, a longitudinal study indicated failure to gain bone at the expected rate in youths (21).

These findings can be extrapolated to the adult population, since it has been demonstrated through anterior research that adults with CF present bone disease (16, 21, 23, 24). In a systematic review and meta-analysis in young adults with CF, the prevalence of osteoporosis was 23.5%, the prevalence of osteopenia was 38.0%, and the prevalence of vertebral and non-vertebral fractures were 14.0% and 19.7%, respectively (13). In this sense, a longitudinal study showed inadequate values of aBMD in adults (21).

These discrepancies and the fact that our meta-analyses did not show differences in aBMD between groups may in part reflect our sample characteristics since participants

with CF remained on their standard meds as part of their usual treatment regimen, which included daily multivitamin and mineral supplements as ADEK vitamins, calcium supplementation, and use of pancreatic enzyme supplements, mainly (40-43). In addition, our sample of healthy participants were mostly physically inactive (44, 45, 49, 51, 55, 57-59, 61, 64, 65, 67, 72) and/or did not meet the minimum calcium and/or vitamin D intake (46, 47, 52-54, 59, 66, 68). It is known that nutritional status is a major determinant of aBMD (42), importantly vitamin D and K deficiencies, and a negative calcium balance (27). In other words, CF children who receive the nutritional supplementation as part of their medical treatment do not have their aBMD negatively affected. Similarly, young people with CF has affected bone accrual in those with the poorest nutritional status (42). So, aBMD is usually normal in children with CF with no nutritional deficit (20), which is the case in 4 out of 6 studies (40-43), omitting that information in the other 2 studies (21, 39). Further, it has been demonstrated that calcium absorption is normal in children with CF (40) and that those who have never received steroid treatment could also present bone deficit (43). So, steroid treatment is not determinant in the development of bone deficit (43). In 4 out of 6 studies (21, 39, 41, 42), some of the patients received steroid treatment while in the other two studies they did not receive (40, 43)

We must also bear in mind that they are children and, therefore, they are growing. The greatest growth and skeletal maturation occurs at the end of puberty when ~51% of the peak bone mass is attained (77). In this regard, it has been demonstrated that total body bone mineral content increases across pubertal groups, as a consequence of pubertal growth (41). Therefore, it is important to optimize bone health in children, adolescents and adults with CF through strategies that include a nutritional plan, vitamin K, vitamin D and calcium supplementation if necessary, and as well as weight bearing exercise (27).

Exercise during childhood, especially high impact sports (such as football, handball or basketball) have been related to improvements in aBMD (78, 79), and strength at loaded sites (80). Additionally, it is recommended to monitor patients with CF through DXA scanners to have a follow-up of their bone health according to the European Cystic Fibrosis Society (81).

Some limitations need to be acknowledged. First, the limited number of published studies investigating bone health in children and/or adolescence with CF must be taken into account. For this reason, confidence intervals are large compared to the studies in healthy children and adolescents. Second, data extraction were non-blinded, which is a potential source of bias. Third, 66.7% of the CF studies and a 44.8% of the healthy studies presented moderate risk of bias. Fourth, the use of covariates in the studies was heterogeneous, although we have always tried to analyse raw data. Finally, the majority of the studies did not present a sample size justification, and had shortcomings in the blinding domain.

In conclusion, our meta-analysis showed that aBMD values do not differ between well-nourished children and adolescents with CF and those from their healthy peers. This underlines that in spite of the problems associated with this disease, correct supplementation strategies and clinical care may counteract the possible detrimental consequences of CF on bone health during growth. In addition, long-term physical activity programs may further protect against the sequels of CF on bone mass.

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Table 1. Characteristics of studies included in the systematic review and meta-analysis in cystic fibrosis participants.

Study (year)	Country	Study design	Population characteristics at baseline						Outcome		
			Age [years (mean ± SD)]	Sample size [n (% male)]	BMI [kg/m^2 (mean ± SD)]	Stature [cm (mean ± SD)]	Weight [kg (mean ± SD)]	Type of population	Method	Baseline bone	Follow-up bone
Bhudhikanok et al. (1998)	USA	Longitudinal study (1.5 years)	<u>Males</u> 11.8 ± 2.7 <u>Females</u> 12.1 ± 2.7	20 (45%)	<u>Males</u> 18.5 ± 3.0 <u>Females</u> 16.2 ± 2.3	<u>Males</u> 146 ± 18 <u>Females</u> 145 ± 15	<u>Males</u> 41.0 ± 16.4 <u>Females</u> 35.1 ± 11.2	Patients with cystic fibrosis	Hologic QDR 1000W dual-energy x-ray absorptiometry scanner (Hologic Corporation, Waltham, Mass)	<u>Males (mean ± SD):</u> WB BMD (g/cm^2): 0.855 ± 0.106 LS BMD (g/cm^2): 0.661 ± 0.140 FN BMD (g/cm^2): 0.706 ± 0.114 <u>Females (mean ± SD):</u> WB BMD (g/cm^2): 0.815 ± 0.133 LS BMD (g/cm^2): 0.704 ± 0.210 FN BMD (g/cm^2): 0.616 ± 0.146	<u>Males (mean ± SD):</u> WB BMD (g/cm^2): 0.864 ± 0.103 LS BMD (g/cm^2): 0.678 ± 0.116 FN BMD (g/cm^2): 0.718 ± 0.113 <u>Females (mean ± SD):</u> WB BMD (g/cm^2): 0.829 ± 0.144 LS BMD (g/cm^2): 0.731 ± 0.227 FN BMD (g/cm^2): 0.637 ± 0.182
Colombo et al. (2005)	Italy	Longitudinal study (5 years)	11.5 ± 1.6	4 (75%)	16.9 ± 2.1	142.0 ± 5.0	34.0 ± 4.0	Liver transplant patients with cystic fibrosis	Hologic QDR 2000 dual-energy x-ray absorptiometry scanner (Hologic Inc., Bedford, MA, USA).	<u>(Mean ± SD):</u> WB BMD (g/cm^2): 0.810 ± 0.122	<u>(Mean ± SD):</u> WB BMD (g/cm^2): 0.880 ± 0.106
Colombo et al. (2005)	Italy	Longitudinal study (4.6 years)	11.9 ± 4.4	5 (60%)	17.0 ± 2.5	141.0 ± 22.6	37.9 ± 12.8	Nontransplanted patients with cystic fibrosis	Hologic QDR 2000 dual-energy x-ray absorptiometry scanner (Hologic Inc., Bedford, MA, USA).	<u>(Mean ± SD):</u> WB BMD (g/cm^2): 0.854 ± 0.073	<u>(Mean ± SD):</u> WB BMD (g/cm^2): 0.906 ± 0.078
Hillman et al. (2008)	USA	Longitudinal study	9.1 ± 2.3	9 (NR)	15.9 ± 1.1	134 ± 14	29.3 ± 7.5	Patients with cystic fibrosis	Hologic 1000W dual-energy x-	<u>Changes (mean ± SD):</u>	

		(9 months)	(pero es de todos los sujetos, ya que no muestran la edad sólo del grupo placebo)		(igual que con la edad)	(igual que con la edad)	(igual que con la edad)		ray absorptiometry scanner	WB BMD (g/cm^2): 0.033 ± 0.027 LS BMD (g/cm^2): 0.041 ± 0.045	
Schulze et al. (2006)	USA	Longitudinal study (1-4 years)	12.1 ± 3.2	18 (0%)	18.0 ± 3.0	146 ± 15	39.6 ± 13.9	Patients with cystic fibrosis	Hologic QDR-4500A dual-energy x-ray absorptiometry scanner	Z-score (mean ± SD): LS BMD: -0.40 ± 1.13	Z-score (mean ± SD): LS BMD: -0.46 ± 0.94
Sharma et al. (2017)	New Zealand	Longitudinal study (2 years)	12.1 ± 2.0	40 (0%)	Z-score: -0.17 ± 1.05	Z-score: -0.49 ± 0.88	Z-score: -0.36 ± 0.93	Patients with cystic fibrosis	Lunar Prodigy dual-energy x-ray absorptiometry scanner (GE Health Care)	Z-score (mean ± SD): LS BMD: -0.94 ± 0.88	Z-score (mean ± SD): LS BMD: -1.13 ± 1.0
Ujhelyi et al. (2004)	Hungary	Longitudinal study (2 years)	8.3 (4 - 12)	11 (63.6%)	NR	115.1 ± 9.1	19.5 ± 4.7	Patients with cystic fibrosis	Dual x-ray absorptiometry (Hologic QDR 4500C, Hologic, Waltham, MA, U.S.A.)	Changes (mean ± SD): LS BMD (g/cm^2): 0.04 ± 0.04 FN BMD (g/cm^2): 0.08 ± 0.06	
Ujhelyi et al. (2004)	Hungary	Longitudinal study (2 years)	14.9 (8 - 19)	16 (56.3%)	NR	149.0 ± 16.9	37.0 ± 11.8	Patients with cystic fibrosis	Dual x-ray absorptiometry (Hologic QDR 4500C, Hologic, Waltham, MA, U.S.A.)	Changes (mean ± SD): LS BMD (g/cm^2): 0.10 ± 0.07 FN BMD (g/cm^2): 0.07 ± 0.07	
Not reported: NR											

Table 2. Characteristics of studies included in the systematic review and meta-analysis with healthy participants.

Study (year)	Country	Study design	Population characteristics (baseline)						Outcome		
			Age [years (mean ± SD)]	Sample size [n (% male)]	BMI [kg/m^2 (mean ± SD)]	Stature [cm (mean ± SD)]	Weight [kg (mean ± SD)]	Type of population	Method	Baseline bone	Follow-up bone
Agostinete et al. (2016)	Brazil	A 9-mo follow-up	11.9 ± 2.2	13 (100%)	NR	154.5 ± 13.1	NR	Healthy male adolescents	Lunar DPX-NT dual-energy x-ray absorptiometry scanner	Mean ± SD: WB BMD (g/cm^2): 1.001 ± 0.100 LS BMD (g/cm^2): 0.857 ± 0.130	Mean ± SD: WB BMD (g/cm^2): 1.041 ± 1.106 LS BMD (g/cm^2): 0.901 ± 0.147
Ara et al. (2006)	Spain	3.3-year follow-up period	9.3 ± 1.6	16 (100%)	16.9 ± 2.2	136.5 ± 10.8	31.9 ± 7.6	Healthy male children and adolescents	Hologic QDR-1500 dual-energy x-ray absorptiometry scanner	Changes (mean ± SD): WB BMD (g/cm^2): 9.25 ± 4.34	
Bonjour et al. (1997)	Switzerland	48 wk follow-up	7.9 ± 0.1	53 (0%)	16.6 ± 0.3	127.2 ± 0.8	26.9 ± 0.6	Healthy prepubertal caucasian girls	Hologic QDR-2000 dual-energy x-ray absorptiometry scanner	Mean ± SEM: LS BMD (g/cm^2): 0. 615 ± 0.008 FN BMD (g/cm^2): 0. 622 ± 0.009	Mean ± SEM: LS BMD (g/cm^2): 0. 638 ± 0.008 FN BMD (g/cm^2): 0. 635 ± 0.009
Cameron et al. (2004)	Australia	A 6-mo follow-up	10.3 ± 1.5	51 (0%)	NR	141.62 ± 9.45	37.5 ± 9.5	Healthy australian Twins	QDR 1000W dual-energy x-ray absorptiometry scanner	Mean ± SD: LS BMD (g/cm^2): 0.697 ± 0.085 FN BMD (g/cm^2): 0.697 ± 0.084	Mean ± SD: LS BMD (g/cm^2): 0.724 ± 0.097 FN BMD (g/cm^2): 0.714 ± 0.615
Cameron et al. (2004) Mismo estudio que el anterior	Australia	A 12-mo follow-up	10.4 ± 1.5	48 (0%)	NR	141.60 ± 9.52	37. ± 9.8	Healthy australian Twins	QDR 1000W dual-energy x-ray absorptiometry scanner	Mean ± SD: LS BMD (g/cm^2): 0.697 ± 0.085 FN BMD (g/cm^2): 0.697 ± 0.084	Mean ± SD: LS BMD (g/cm^2): 0.759 ± 0.114 FN BMD (g/cm^2): 0.742 ± 0.107
Cameron et al. (2004) Mismo estudio que el anterior	Australia	A 18-mo follow-up	10.4 ± 1.5	42 (0%)	NR	142.12 ± 9.18	37.6 ± 9.5	Healthy australian Twins	QDR 1000W dual-energy x-ray absorptiometry scanner	Mean ± SD: LS BMD (g/cm^2): 0.697 ± 0.085 FN BMD (g/cm^2): 0.697 ± 0.084	Mean ± SD: LS BMD (g/cm^2): 0.804 ± 0.129 FN BMD (g/cm^2): 0.765 ± 0.112

Cameron et al. (2004) Mismo estudio que el anterior	Australia	A 24-mo follow-up	10.6 ± 1.5	24 (0%)	NR	141.80 ± 9.12	37.1 ± 7.3	Healthy australian Twins	QDR 1000W dual-energy x-ray absorptiometry scanner	Mean ± SD: LS BMD (g/cm^2): 0.697 ± 0.085 FN BMD (g/cm^2): 0.697 ± 0.084	Mean ± SD: LS BMD (g/cm^2): 0.833 ± 0.142 FN BMD (g/cm^2): 0.816 ± 0.131
Chevalley et al. (2011)	Switzerland	A 12-y follow-up	7.9 ± 0.5	124 (0%)	16.2 ± 1.8	127.7 ± 5.9	26.5 ± 4.1	Healthy girls	Hologic QDR-4500 dual-energy x-ray absorptiometry scanner	Mean ± SD: FN BMD (g/cm^2): 0.634 ± 0.074	Mean ± SD: FN BMD (g/cm^2): (after 1 year) 0.647 ± 0.075 FN BMD (g/cm^2): (after 2 years) 0.675 ± 0.078 FN BMD (g/cm^2): (after 4 years) 0.751 ± 0.103 FN BMD (g/cm^2): (after 8 years) 0.867 ± 0.111 FN BMD (g/cm^2): (after 12 years) 0.858 ± 0.108
Erlandsson et al. (2012)	Canada	A 14-y follow-up	11.9 ± 1.7	22 (0%)	NR	151.6 ± 11.7	44.3 ± 11.9	Healthy white girls	Hologic 2000 QDR dual-energy x-ray absorptiometry scanner	Mean ± SD: WB BMD (g/cm^2): 0.8 ± 0.1 LS BMD (g/cm^2): 0.7 ± 0.2 FN BMD (g/cm^2): 0.7 ± 0.1	Mean ± SD: WB BMD (g/cm^2): 1.1 ± 0.1 LS BMD (g/cm^2): 1.0 ± 0.1 FN BMD (g/cm^2): 0.9 ± 0.6
Fuchs et al. (2001)	USA	A 7-mo follow-up	7.6 ± 0.2	44 (59.09%) 26 chicos y 18 chicas	NR	126.8 ± 1.2	NR	Healthy school children	Hologic QDR/4500-A dual-energy x-ray absorptiometry scanner	Mean ± SEM: LS BMD (g/cm^2): 0.550 ± 0.008 FN BMD (g/cm^2): 0.613 ± 0.010	Mean ± SEM: LS BMD (g/cm^2): 0.571 ± 0.008 FN BMD (g/cm^2): 0.635 ± 0.009

Gómez-Brutón et al. (2017)	Spain	An 8-mo follow-up	14.1 ± 2.3	28 (57.14%) 16 chicos y 12 chicas	20.4 ± 3.3	159.8 ± 11.7	52.8 ± 13.4	Healthy Caucasian adolescents	QDR 4500-Explorer dual-energy x-ray absorptiometry scanner	Mean ± SD: WB BMD (g/cm^2): (less head) 0.889 ± 0.076 LS BMD (g/cm^2): 0.861 ± 0.128 FN BMD (g/cm^2): 0.833 ± 0.116	Mean ± SD: WB BMD (g/cm^2): (less head) 0.905 ± 0.075 LS BMD (g/cm^2): 0.886 ± 0.122 FN BMD (g/cm^2): 0.844 ± 0.110
Lambert et al. (2008)	United Kingdom	an 18-mo randomized controlled trial with 2-y follow-up	11.4 ± 0.5	44 (0%)	19.0 ± 3.1	149.8 ± 8.2	43.2 ± 10.1	Healthy white girls	QDR 4500A dual-energy x-ray absorptiometry scanner	Mean ± SD: WB BMD (g/cm^2): 0.88 ± 0.06 LS BMD (g/cm^2): 0.70 ± 0.11	Mean ± SD: WB BMD (g/cm^2): 0.954 ± 0.004 LS BMD (g/cm^2): 0.831 ± 0.007
Mackelvie et al. (2002)	Canada	A 7-Month Randomized Controlled	10.3 ± 0.7	60 (100%)	18.0 ± 4.0	141.8 ± 7.1	36.6 ± 10.1	Healthy Asian and white children (North American or European origin)	QDR 4500W dual-energy x-ray absorptiometry scanner	Changes (mean ±95%CI): LS BMD (g/cm^2): 0.020 (0.015-0.025) FN BMD (g/cm^2): 0.014 (0.009-0.019)	
Markovic et al. (2005)	USA	4-y follow-up	10.8 ± 0.7	123 (0%)	NR	145.2 ± 7.0	40.2 ± 9.0	Healthy Caucasian girls	GE-Lunar DPX-L dual-energy x-ray absorptiometry scanner	Changes (mean ± SD): WB BMD (g/cm^2): 0.204 ± 0.035	
Markovic et al. (2005) Mismo estudio que el anterior	USA	7-y folow-up	10.8 ± 0.7	100 (0%)	NR	145.2 ± 7.0	40.2 ± 9.0	Healthy Caucasian girls	GE-Lunar DPX-L dual-energy x-ray absorptiometry scanner	Changes (mean ± SD): WB BMD (g/cm^2): 0.263 ± 0.044	
Nickols et al. (1999)	USA	6-month follow-up	10.1 ± 0.3	9 (0%)	NR	138.9 ± 2.4	30.3 ± 1.7	Healthy premenarcheal girls	QDR-1000 W dual-energy x-ray	Mean ± SEM: WB BMD (g/cm^2): 0.835 ± 0.012	Mean ± SEM: WB BMD (g/cm^2): 0.845 ± 0.013

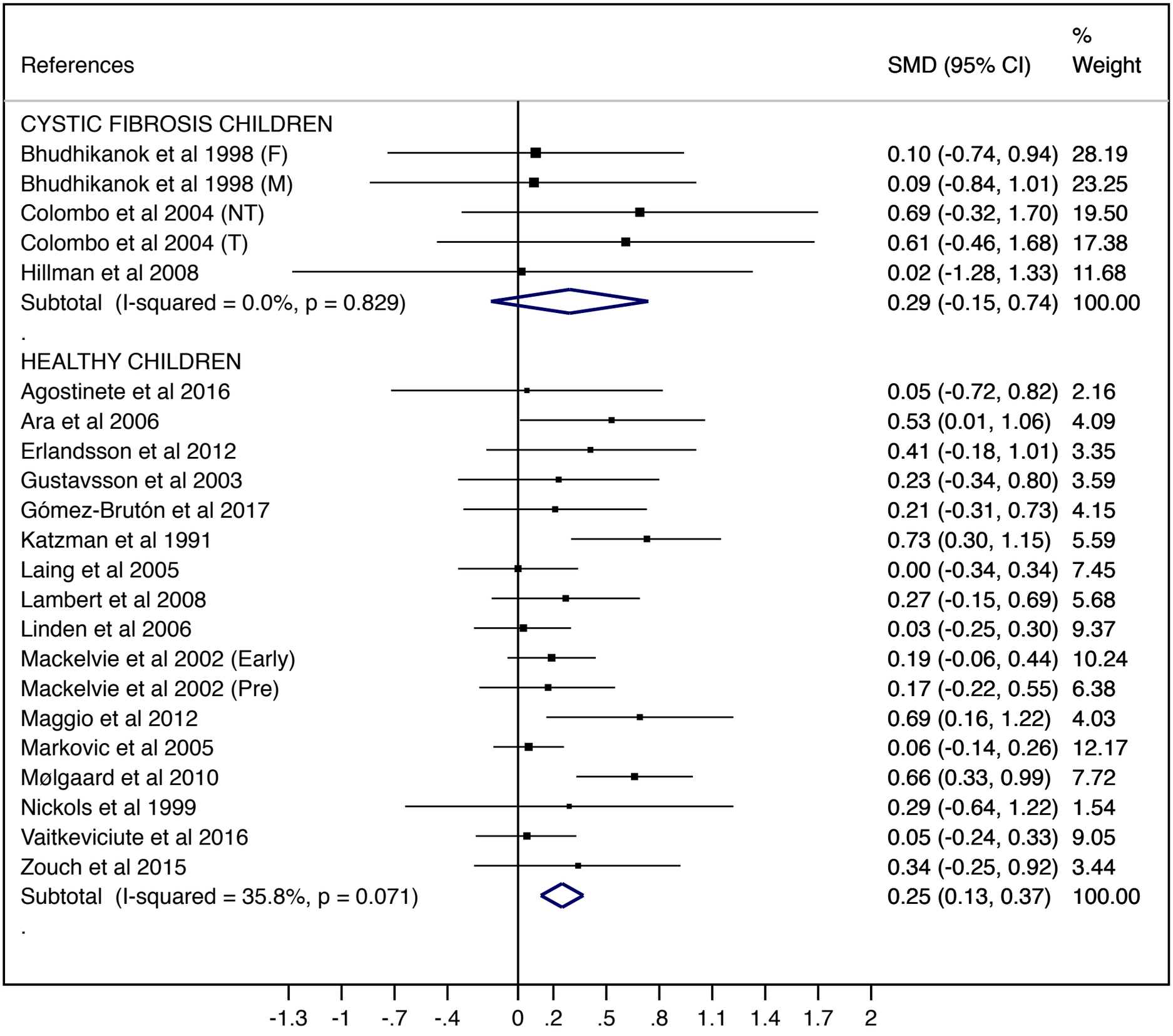
								Caucasian	absorptiometry scanner	LS BMD (g/cm^2): 0.620 ± 0.019 FN BMD (g/cm^2): 0.647 ± 0.023	LS BMD (g/cm^2): 0.6412± 0.020 FN BMD (g/cm^2): 0.663 ± 0.024
Nickols et al. (1999) Mismo estudio que el anterior	USA	12-month follow-up	10.1 ± 0.3	9 (0%)	NR	138.9 ± 2.4	30.3 ± 1.7	Healthy premenarcheal girls Caucasian	QDR-1000 W dual-energy x-ray absorptiometry scanner	<u>Mean ± SEM:</u> WB BMD (g/cm^2): 0.835 ± 0.012 LS BMD (g/cm^2): 0.6200± 0.019 FN BMD (g/cm^2): 0.647 ± 0.023	<u>Mean ± SEM:</u> WB BMD (g/cm^2): 0.864 ± 0.014 LS BMD (g/cm^2): 0.666 ± 0.022 FN BMD (g/cm^2): 0.675 ± 0.025
Vaitkeviciute et al. (2016)	Estonia	12-month follow-up	11.9 ± 0.6	96 (100%)	20.5 ± 5.2	153.8 ± 7.4	49.3 ± 16.0	Healthy school children	Lunar DPX-IQ dual-energy x-ray absorptiometry scanner	<u>Mean ± SD:</u> WB BMD (g/cm^2): 0.983 ± 0.069 LS BMD (g/cm^2): 0.831 ± 0.097 FN BMD (g/cm^2): 0.895 ± 0.086	<u>Mean ± SD:</u> WB BMD (g/cm^2): 1.018 ± 0.081 LS BMD (g/cm^2): 0.890 ± 0.121 FN BMD (g/cm^2): 0.940 ± 0.103
Vaitkeviciute et al. (2016) Mismo estudio que el anterior	Estonia	24-month follow-up	11.9 ± 0.6	96 (100%)	20.5 ± 5.2	153.8 ± 7.4	49.3 ± 16.0	Healthy school children	Lunar DPX-IQ dual-energy x-ray absorptiometry scanner	<u>Mean ± SD:</u> WB BMD (g/cm^2): 0.983 ± 0.069 LS BMD (g/cm^2): 0.831 ± 0.097 FN BMD (g/cm^2): 0.895 ± 0.086	<u>Mean ± SD:</u> WB BMD (g/cm^2): 1.018 ± 0.081 LS BMD (g/cm^2): 0.890 ± 0.121 FN BMD (g/cm^2): 0.940 ± 0.103
Zouch et al. (2015)	France	A 3-Yr Longitudinal Study	11.74 ± 0.64	23 (100%)	18.6 ± 2.9	152.0 ± 6.0	42.6 ± 8.3	Healthy Caucasian boys	Hologic WB Delphi dual-energy x-ray absorptiometry scanner	<u>Mean ± SD:</u> WB BMD (g/cm^2): 0.902 ± 0.042 LS BMD (g/cm^2): 0.679 ± 0.071 FN BMD (g/cm^2): 0.753 ± 0.065	<u>Mean ± SD:</u> WB BMD (g/cm^2): 1.010 ± 0.087 LS BMD (g/cm^2): 0.843 ± 0.121 FN BMD (g/cm^2): 0.840 ± 0.100
Bradney et al. (1998)	Australia/ USA	8-month follow-up	10.3 ± 0.2	19 (100%)	NR	142.2 ± 1.3	40.1 ± 1.6	Healthy school children	Lunar DPX-L dual-energy x-ray	<u>Mean ± SEM:</u> WB BMD (g/cm^2): 0.92 ± 0.01 LS BMD (g/cm^2):	<u>Changes per month (mean ± SEM):</u> WB BMD (g/cm^2): 0.002 ± 0.001

									absorptiometry scanner	0.77 ± 0.02	LS BMD (g/cm^2): 0.002 ± 0.001
Johannsen et al. (2003)	USA	12-week intervention randomized trial	10.0 ± 5.1	26 (45.2%)	NR	136.6 ± 30.7	39.3 ± 20.7	Healthy children	Hologic 4500A dual-energy x-ray absorptiometry scanner	<u>Changes (mean ± SEM):</u> LS BMD (g/cm^2): 0.009 ± 0.004 FN BMD (g/cm^2): 0.001 ± 0.005	
Laing et al. (2005)	USA	A 24-month quasi-experimental	6.0 ± 1.49	78 (0%)	17.3 ± 2.88	119.0 ± 11.8	25.2 ± 7.6	Healthy females	Hologic QDR-1000W dual-energy x-ray absorptiometry scanner	<u>Mean ± SD:</u> WB BMD (g/cm^2): 0.669 ± 0.06 LS BMD (g/cm^2): 0.557 ± 0.07	<u>Mean ± SD:</u> WB BMD (g/cm^2): 0.736 ± 0.07 LS BMD (g/cm^2): 0.609 ± 0.08
Linden et al. (2006)	Sweden	2-year prospective controlled exercise intervention trial	7.9 ± 0.6	50 (0%)	NR	129.1 ± 7.9	27.4 ± 5.5	Healthy elementary schools in a middle-class area	Lunar DPX-L dual-energy x-ray absorptiometry scanner	<u>Mean ± SD:</u> WB BMD (g/cm^2): 0.84 ± 0.05 LS BMD (g/cm^2): 0.70 ± 0.08 FN BMD (g/cm^2): 0.71 ± 0.10	<u>Changes per year (mean ± SD):</u> WB BMD (g/cm^2): 0.024 ± 0.009 LS BMD (g/cm^2): 0.026 ± 0.015 FN BMD (g/cm^2): 0.040 ± 0.040
MacKelvie et al.(2001)	Canada	7-month randomized, prospective, school-based intervention	Prepubertal: 10.1 ± 0.5 Early pubertal: 10.5 ± 0.6	Prepubertal: 26 (0%) Early pubertal: 64 (0%)	NR	Prepubertal: 137.3 ± 6.2 Early pubertal: 145.6 ± 6.4	Prepubertal: 31.1 ± 5.6 Early pubertal: 41.3 ± 8.3	Healthy Asian and white children (North American or European origin)	Hologic QDR 4500 W dual-energy x-ray absorptiometry scanner	<u>Prepubertal (mean ± SD):</u> WB BMD (g/cm^2): 0.860 ± 0.040 LS BMD (g/cm^2): 0.630 ± 0.060 FN BMD (g/cm^2): 0.630 ± 0.070 <u>Early pubertal (mean ± SD):</u> WB BMD (g/cm^2):	<u>Prepubertal changes (mean ± 95%CI):</u> WB BMD (g/cm^2): 0.017 (0.011-0.023) LS BMD (g/cm^2): 0.027 (0.019-0.034) FN BMD (g/cm^2): 0.024 (0.016-0.031)

										0.870 ± 0.070 LS BMD (g/cm^2): 0.690 ± 0.100 FN BMD (g/cm^2): 0.670 ± 0.090	<u>Early pubertal (mean ± SD):</u> WB BMD (g/cm^2): 0.030 (0.025-0.035) LS BMD (g/cm^2): 0.044 (0.038-0.049) FN BMD (g/cm^2): 0.034 (0.028-0.039)
McKay et al. (2000)	Canada	A 8 months randomized school-based exercise intervention study	6.9 to 10.2 years	81 (NR)	NR	133.9 ± 0.7	30.5 ± 0.8	Healthy Asian and white children (North American or European origin)	Hologic QDR 4500 W dual-energy x-ray absorptiometry scanner	<u>Mean ± SEM:</u> WB BMD (g/cm^2): 0.807 ± 0.006 LS BMD (g/cm^2): 0.581 ± 0.007 FN BMD (g/cm^2): 0.642 ± 0.008	<u>Mean ± SEM:</u> WB BMD (g/cm^2): 0.818 ± 0.006 LS BMD (g/cm^2): 0.592 ± 0.007 FN BMD (g/cm^2): 0.661 ± 0.009
Moriss et al. (1997)	Australia	Prospective Ten-Month Exercise Intervention	9.5 ± 0.9	38 (0%)	NR	138.6 ± 6.4	34.8 ± 5.2	Healthy school girls	Hologic QDR-2000+ dual-energy x-ray absorptiometry scanner	<u>Mean ± SEM:</u> WB BMD (g/cm^2): 0.810 ± 0.01 LS BMD (g/cm^2): 0.637 ± 0.01 FN BMD (g/cm^2): 0.690 ± 0.07	<u>Changes (mean± SEM):</u> WB BMD (g/cm^2): 0.010 ± 0.01 LS BMD (g/cm^2): 0.008 ± 0.05 FN BMD (g/cm^2): 0.012 ± 0.03
Nichols et al. (2001)	USA	15 months follow-up	15.7 ± 0.1	11 (0%)	NR	158.2 ± 3.1	63.8 ± 5.2	Healthy females	Lunar DPX dual-energy x-ray absorptiometry scanner	<u>Mean ± SD:</u> WB BMD (g/cm^2): 1.111 ± 0.066 LS BMD (g/cm^2): 1.158 ± 0.135 FN BMD (g/cm^2):	<u>Mean ± SD:</u> WB BMD (g/cm^2): 1.129 ± 0.065 LS BMD (g/cm^2): 1.190 ± 0.125 FN BMD (g/cm^2):

										1.034 ± 0.086	1.048 ± 0.075
Van Langendonck et al. (2003)	Belgium	9 months follow-up	8.7 ± 0.7	21 (0%)	NR	132.22 ± 6.37	28.8 ± 4.5	Healthy female twins	Hologic QDR-4500A dual-energy x-ray absorptiometry scanner	Mean ± SD: WB BMD (g/cm^2): 0.850 ± 0.030 LS BMD (g/cm^2): 0.850 ± 0.030 FN BMD (g/cm^2): 0.630 ± 0.060	Changes (mean± SD): WB BMD (g/cm^2): 0.020 ± 0.020 LS BMD (g/cm^2): 0.010 ± 0.020 FN BMD (g/cm^2): 0.020 ± 0.020
Chevalley et al. (2011)	Switzerland	an 8-yr cohort study	7.4 ± 0.4	89 (100%)	15.9 ± 2.0	125.5 ± 6.2	25.2 ± 5.0	Healthy prepubertal Caucasian boys	Hologic QDR 4500 dual-energy x-ray absorptiometry scanner	Mean ± SD: LS BMD (g/cm^2): 0.568 ± 0.052 FN BMD (g/cm^2): 0.688 ± 0.070	Mean ± SD: LS BMD (g/cm^2): 0.918 ± 0.135 FN BMD (g/cm^2): 0.901 ± 0.133
Gustavsson et al. (2003)	Sweden	3 years follow-up	16.1 ± 0.6	24 (100%)	NR	179.0 ± 6.0	69.2 ± 10.1	Healthy Caucasian boys	Lunar DPX-L dual-energy x-ray absorptiometry scanner	Mean ± SD: WB BMD (g/cm^2): 1.15 ± 0.11 LS BMD (g/cm^2): 1.10 ± 0.14 FN BMD (g/cm^2): 1.13 ± 0.15	Mean ± SD: WB BMD (g/cm^2): 1.26 ± 0.09 LS BMD (g/cm^2): 1.24 ± 0.14 FN BMD (g/cm^2): 1.21 ± 0.16
Katzman et al. (1991)	USA	2 years follow-up	14.3 ± 3.6	45 (0%)	20.0 ± 2.9	158.0 ± 13.2	50.6 ± 12.7	Healthy adolescent females	Hologic QDR 1000W dual-energy x-ray absorptiometry scanner	Mean ± SD: WB BMD (g/cm^2): 0.904 ± 0.130 LS BMD (g/cm^2): 1.009 ± 0.155	Mean ± SD: WB BMD (g/cm^2): 0.993 ± 0.114 LS BMD (g/cm^2): 1.005 ± 0.142
Maggio et al. (2012)	Switzerland	9 month follow-up	10.5 ± 3.0	17 (47%)	17.8 ± 2.9	143.1 ± 19.1	38.3 ± 15.7	Healthy children	GE Lunar Prodigyi dual-energy x-ray absorptiometry scanner	Mean ± SD: WB BMD (g/cm^2): 0.94 ± 0.13 LS BMD (g/cm^2): 0.83 ± 0.25 FN BMD (g/cm^2): 0.86 ± 0.17	Changes (mean± SD): WB BMD (g/cm^2): 0.020 ± 0.007 LS BMD (g/cm^2): 0.033 ± 0.014 FN BMD (g/cm^2): 0.025 ± 0.019

Mølgaard et al. (2010)	Denmark	12 month follow-up	11.4 ± 0.2	74 (0%)	NR	150.1 ± 6.9	40.5 ± 7.9	Healthy Danish Caucasian girls	Hologic 1000/W dual-energy x-ray absorptiometry scanner	Mean ± SD: WB BMD (g/cm^2): 0.863 ± 0.064 LS BMD (g/cm^2): 0.697 ± 0.102	Mean ± SD: WB BMD (g/cm^2): 0.909 ± 0.075 LS BMD (g/cm^2): 0.788 ± 0.121
Nogueira et al. (2015)	Australia	A 9-month, cluster-controlled trial	10.7 ± 0.6	68 (100%)	NR	143.7 ± 6.2	39.6 ± 9.2	Healthy school children	Norland Medical XR800 dual-energy x-ray absorptiometry scanner	Mean ± SD: WB BMD (g/cm^2): 0.765 ± 0.083 LS BMD (g/cm^2): 0.674 ± 0.123 FN BMD (g/cm^2): 0.803 ± 0.116	Mean ± SD: WB BMD (g/cm^2): 0.806 ± 0.103 LS BMD (g/cm^2): 0.705 ± 0.150 FN BMD (g/cm^2): 0.843 ± 0.134
NR: not reported											


References
SMD (95% CI)
% Weight
CYSTIC FIBROSIS CHILDREN
Bhudhikanok et al 1998 (F) 0.10 (-0.74, 0.94) 28.19
Bhudhikanok et al 1998 (M) 0.09 (-0.84, 1.01) 23.25
Colombo et al 2004 (NT) 0.69 (-0.32, 1.70) 19.50
Colombo et al 2004 (T) 0.61 (-0.46, 1.68) 17.38
Hillman et al 2008 0.02 (-1.28, 1.33) 11.68
Subtotal (I-squared = 0.0%, p = 0.829) 0.29 (-0.15, 0.74) 100.00
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HEALTHY CHILDREN
Agostinete et al 2016 0.05 (-0.72, 0.82) 2.16
Ara et al 2006 0.53 (0.01, 1.06) 4.09
Erlandsson et al 2012 0.41 (-0.18, 1.01) 3.35
Gustavsson et al 2003 0.23 (-0.34, 0.80) 3.59
Gómez-Brutón et al 2017 0.21 (-0.31, 0.73) 4.15
Katzman et al 1991 0.73 (0.30, 1.15) 5.59
Laing et al 2005 0.00 (-0.34, 0.34) 7.45
Lambert et al 2008 0.27 (-0.15, 0.69) 5.68
Linden et al 2006 0.03 (-0.25, 0.30) 9.37
Mackelvie et al 2002 (Early) 0.19 (-0.06, 0.44) 10.24
Mackelvie et al 2002 (Pre) 0.17 (-0.22, 0.55) 6.38
Maggio et al 2012 0.69 (0.16, 1.22) 4.03
Markovic et al 2005 0.06 (-0.14, 0.26) 12.17
Mølgaard et al 2010 0.66 (0.33, 0.99) 7.72
Nickols et al 1999 0.29 (-0.64, 1.22) 1.54
Vaitkeviciute et al 2016 0.05 (-0.24, 0.33) 9.05
Zouch et al 2015 0.34 (-0.25, 0.92) 3.44
Subtotal (I-squared = 35.8%, p = 0.071) 0.25 (0.13, 0.37) 100.00
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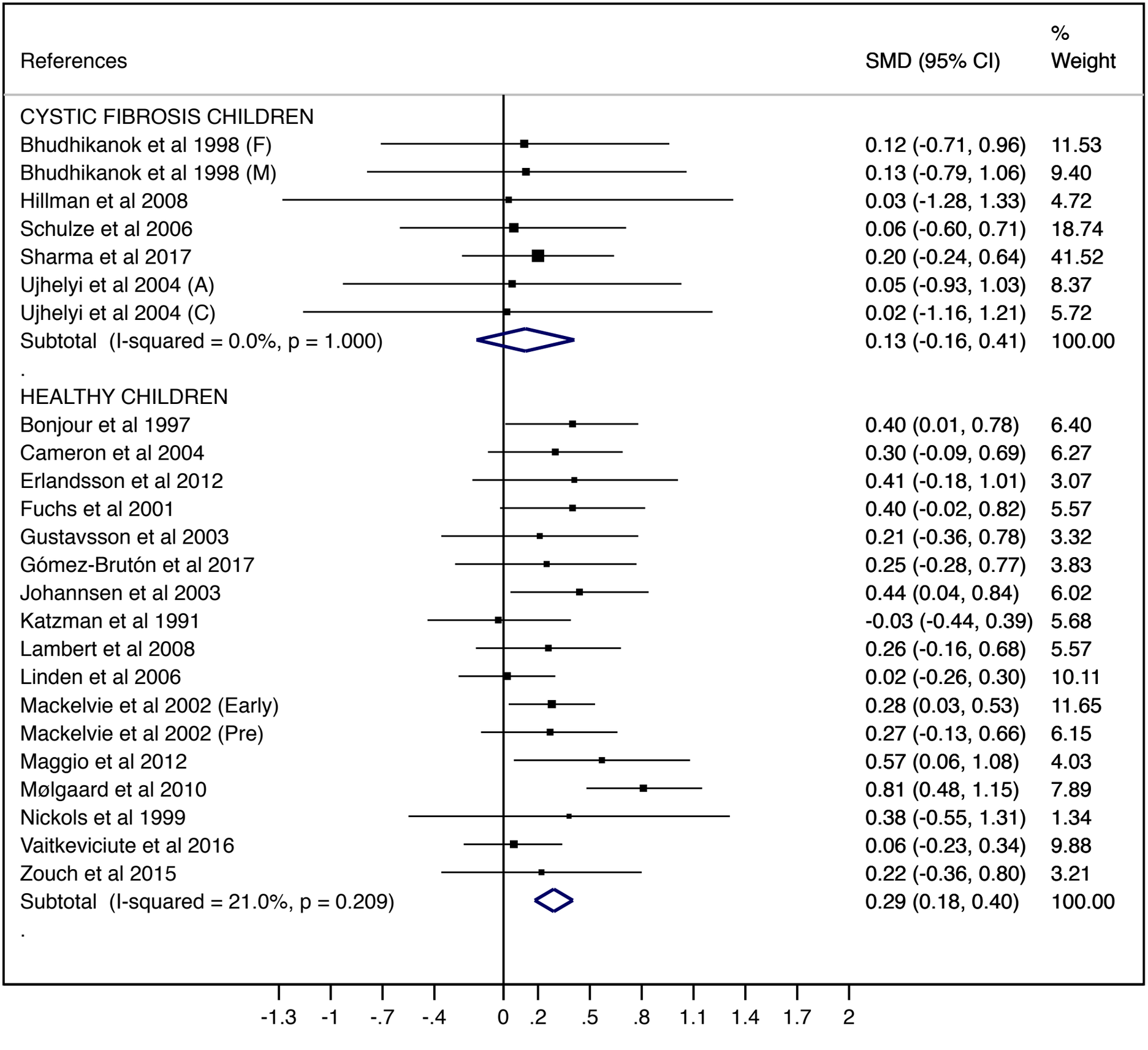
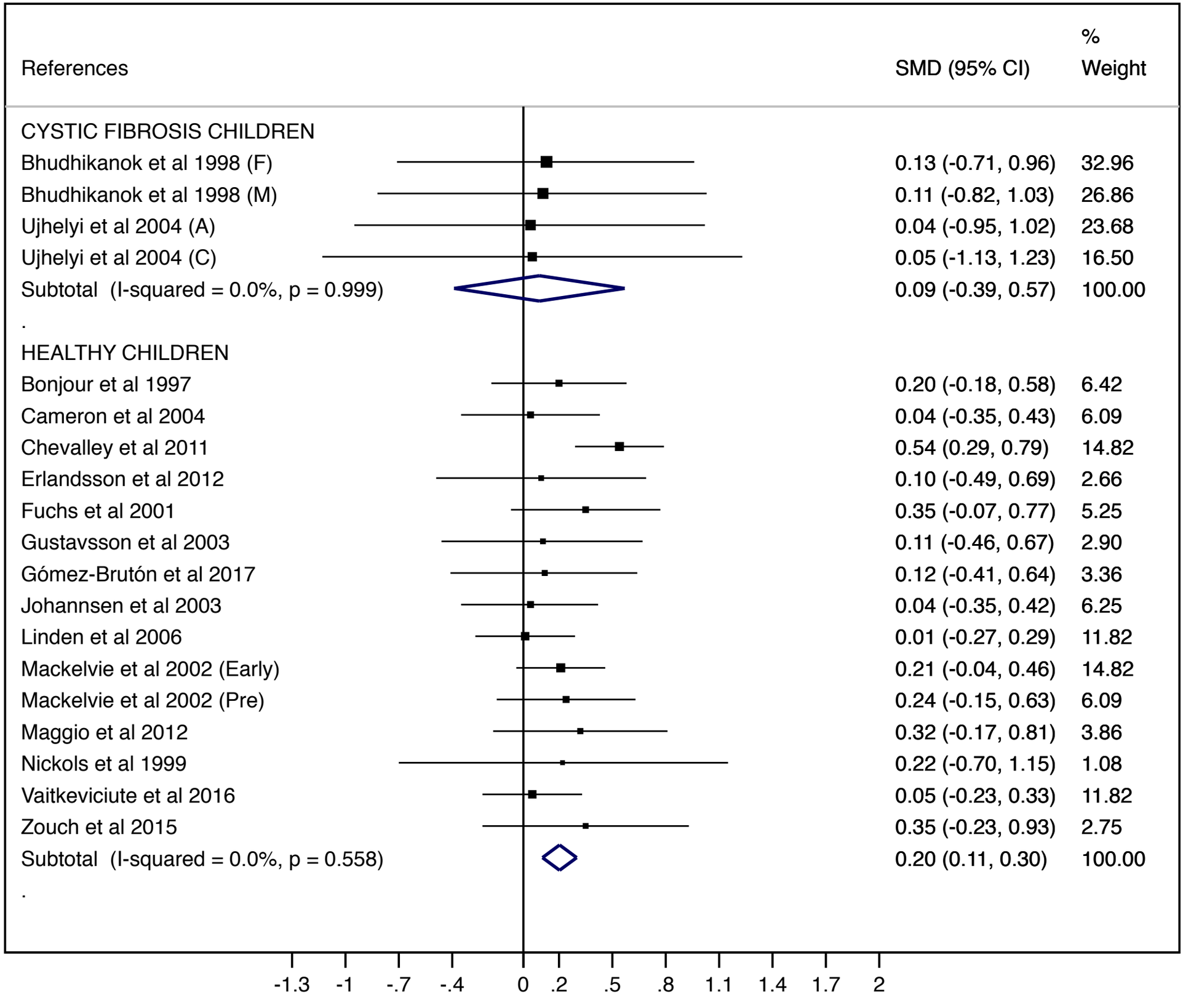
-1.3 -1 -.7 -.4 0 .2 .5 .8 1.1 1.4 1.7 2


References
SMD (95% CI)
% Weight
CYSTIC FIBROSIS CHILDREN
Bhudhikanok et al 1998 (F) 0.12 (-0.71, 0.96) 11.53
Bhudhikanok et al 1998 (M) 0.13 (-0.79, 1.06) 9.40
Hillman et al 2008 0.03 (-1.28, 1.33) 4.72
Schulze et al 2006 0.06 (-0.60, 0.71) 18.74
Sharma et al 2017 0.20 (-0.24, 0.64) 41.52
Ujhelyi et al 2004 (A) 0.05 (-0.93, 1.03) 8.37
Ujhelyi et al 2004 (C) 0.02 (-1.16, 1.21) 5.72
Subtotal (I-squared = 0.0%, p = 1.000) 0.13 (-0.16, 0.41) 100.00
HEALTHY CHILDREN
Bonjour et al 1997 0.40 (0.01, 0.78) 6.40
Cameron et al 2004 0.30 (-0.09, 0.69) 6.27
Erlandsson et al 2012 0.41 (-0.18, 1.01) 3.07
Fuchs et al 2001 0.40 (-0.02, 0.82) 5.57
Gustavsson et al 2003 0.21 (-0.36, 0.78) 3.32
Gómez-Brutón et al 2017 0.25 (-0.28, 0.77) 3.83
Johannsen et al 2003 0.44 (0.04, 0.84) 6.02
Katzman et al 1991 -0.03 (-0.44, 0.39) 5.68
Lambert et al 2008 0.26 (-0.16, 0.68) 5.57
Linden et al 2006 0.02 (-0.26, 0.30) 10.11
Mackelvie et al 2002 (Early) 0.28 (0.03, 0.53) 11.65
Mackelvie et al 2002 (Pre) 0.27 (-0.13, 0.66) 6.15
Maggio et al 2012 0.57 (0.06, 1.08) 4.03
Mølgaard et al 2010 0.81 (0.48, 1.15) 7.89
Nickols et al 1999 0.38 (-0.55, 1.31) 1.34
Vaitkeviciute et al 2016 0.06 (-0.23, 0.34) 9.88
Zouch et al 2015 0.22 (-0.36, 0.80) 3.21
Subtotal (I-squared = 21.0%, p = 0.209) 0.29 (0.18, 0.40) 100.00
-1.3 -1 -.7 -.4 0 .2 .5 .8 1.1 1.4 1.7 2


References
SMD (95% CI)
% Weight
CYSTIC FIBROSIS CHILDREN
Bhudhikanok et al 1998 (F)
0.13 (-0.71, 0.96)
32.96
Bhudhikanok et al 1998 (M)
0.11 (-0.82, 1.03)
26.86
Ujhelyi et al 2004 (A)
0.04 (-0.95, 1.02)
23.68
Ujhelyi et al 2004 (C)
0.05 (-1.13, 1.23)
16.50
Subtotal (I-squared = 0.0%, p = 0.999)
0.09 (-0.39, 0.57)
100.00
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HEALTHY CHILDREN
Bonjour et al 1997
0.20 (-0.18, 0.58)
6.42
Cameron et al 2004
0.04 (-0.35, 0.43)
6.09
Chevalley et al 2011
0.54 (0.29, 0.79)
14.82
Erlandsson et al 2012
0.10 (-0.49, 0.69)
2.66
Fuchs et al 2001
0.35 (-0.07, 0.77)
5.25
Gustavsson et al 2003
0.11 (-0.46, 0.67)
2.90
Gómez-Brutón et al 2017
0.12 (-0.41, 0.64)
3.36
Johannsen et al 2003
0.04 (-0.35, 0.42)
6.25
Linden et al 2006
0.01 (-0.27, 0.29)
11.82
Mackelvie et al 2002 (Early)
0.21 (-0.04, 0.46)
14.82
Mackelvie et al 2002 (Pre)
0.24 (-0.15, 0.63)
6.09
Maggio et al 2012
0.32 (-0.17, 0.81)
3.86
Nickols et al 1999
0.22 (-0.70, 1.15)
1.08
Vaitkeviciute et al 2016
0.05 (-0.23, 0.33)
11.82
Zouch et al 2015
0.35 (-0.23, 0.93)
2.75
Subtotal (I-squared = 0.0%, p = 0.558)
0.20 (0.11, 0.30)
100.00
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-1.3
-1
-.7
-.4
0
.2
.5
.8
1.1
1.4
1.7
2