Quality of life in pediatric asthma patients and their parents: A meta-analysis on 20 years of research

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Abstract

Introduction. This meta-analytic review was conducted to estimate the magnitude of quality of life (QoL) impairments in children/adolescents with asthma and their parents. ***Method.*** A systematic search in four electronic databases revealed 15 quantitative studies published between 1994-2013 that directly compared the QoL of 7- to 18-year-old asthma patients/parents to community/healthy controls. Pooled mean differences (MD) with 95% CI were estimated using the inverse-variance random-effects method. ***Results.*** Pediatric asthma patients (*n* = 1,797) presented lower overall QoL (MD = -7.48, CI = -10.67/ -4.29), physical functioning (MD = -9.36, CI = -11.85/ -6.86), psychological functioning (MD = -5.00, CI = -7.17/ -2.82), and social functioning (MD = -3.76, CI = -5.80/ -1.72), compared to controls (*n* = 13,266). For parents (666 cases and 7,328 controls), asthma was associated with lower physical functioning (MD = -10.15, CI = -12.21/ -8.08). Between-studies heterogeneity was explained by type of informant and selection of controls. ***Conclusion.*** The ascertainment of the magnitude of QoL impairments and the most affected QoL dimensions for pediatric asthma patients/parents may contribute to the outlining of realistic goals for multidisciplinary interventions in healthcare settings and evaluate its cost-effectiveness.

Keywords

Asthma • Children and adolescents • Meta-analysis • Parents • Patient- and parent-reported outcomes • Quality of life

Silva, N., Carona, C., Crespo, C., & Canavarro, M. C. (2015). Quality of life in pediatric asthma patients and their parents: A meta-analysis on 20 years of research. *Expert Review of Pharmacoeconomics & Outcomes Research*, *15*(3), 499-519. doi:10.1586/14737167.2015.1008459

Introduction

Asthma is the most common chronic health condition in childhood, with an estimated worldwide prevalence of 11.6% in 6- to 7-year-old children and 13.7% in 13- to 14-year-old adolescents (Pearce et al., 2007). Defined as a chronic inflammatory disease of the airways, asthma is characterized by episodic exacerbations of shortness of breath, coughing, wheezing, and chest tightness, which may be life threatening and are a major cause of hospitalizations among pediatric patients (Global Initiative for Asthma [GINA], 2008). Additionally, dependence on medication, sleep disturbances, daytime fatigue, and school/work absenteeism and underachievement may also impair the quality of life (QoL) of children and adolescents and their families (Dean et al., 2010; Schmier et al., 2007).

QoL was formally defined by the World Health Organization Quality of Life (WHOQOL) Group, in 1994, as "a person's perception of his/her position in life within the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards, and concerns" (The WHOQOL Group, 1994, p. 28). This definition assumes that QoL is a holistic concept, and it considers both the disease and individual life experiences as influences on physical, psychological and social well-being (Wallander, Schmitt, & Koot, 2001). For QoL assessment in children and adolescents, the World Health Organization (World Health Organization [WHO], 1993) recommends using self-reports whenever possible, as well as developmentally appropriate and cross-culturally comparable instruments. Moreover, generic and specific assessment modules should be used to both allow comparisons between healthy and clinical populations and to ensure sensibility to disease-related impairments and healthcare needs (Wiebe, Guyatt, Weaver, Matijevic, & Sidwell, 2003). Although children as young as 7/8 years old are able to provide reliable reports of subjective QoL (Matza, Swensen, Flood, Secnik, & Leidy, 2004; Ravens-Sieberer et al., 2006), the use of parent-reports as complementary sources of information has been strongly recommended in pediatric contexts, because parents are the main people responsible for clinical decision-making, which is likely to be influenced by their own perceptions of their children's functioning and well-being (Carona, Silva, & Moreira, 2015; Eiser & Morse, 2001).

Over the past 20 years, QoL has emerged as an essential outcome in epidemiological, clinical and health economic/policy research in the context of pediatric chronic conditions (Bullinger, Schmidt, Peterson, & Ravens-Sieberer, 2006; Clarke & Eiser, 2004). However, pediatric asthma research has yielded heterogeneous findings regarding the magnitude of QoL impairments and the QoL domains that are mostly affected in pediatric patients and their parents. Summarizing the results of studies comparing the QoL of children and adolescents with asthma and their parents with age-

matched controls, not only with arbitrary norms (Gerharz, Eiser, & Woodhouse, 2003), is needed to improve current understanding of the consequences of pediatric asthma on children/adolescents' and their parents' overall adaptation, identify specific areas of functioning that should be targeted in multidisciplinary interventions, and evaluate the efficacy of medical treatments and psychosocial interventions. Accordingly, the main objective of this meta-analytic review was to estimate the differences in QoL overall scores and core domains (physical, psychological, social and school functioning; the latter only for pediatric patients) between 7- to 18-year-old children and adolescents with asthma, or parents of children and adolescents with asthma, and community/healthy controls.

Method

Search strategy

To identify literature published between 1994 and 2013, the first author conducted a systematic search in four electronic databases: PubMed (US National Library of Medicine), PsycINFO, SocINDEX and Thomson Reuters' Web of Science. Combinations of the following keywords were searched: "quality of life", "asthma", "child", "adolescent", "youth" and "pediatric". The detailed strategy used for searching the PsycINFO database is given in Table 1. This search strategy was used for all databases, with slight adaptations to fit different web interfaces. The Medical Subject Headings (MeSH terms) were used in the PubMed search. The final search was conducted on January 28-30, 2014. Additionally, the reference lists of all eligible articles were screened to identify other potentially relevant articles.

Table 1 | Strategy used for searching the PsycINFO electronic database

Number	*Search term*
1.	*"Quality of Life"/
2.	asthma.af.
3.	asthma.mp. or exp Asthma/
4.	child*.af.
5.	adolescent*.af.
6.	youth.af.
7.	(pediatric or paediatric).af.
8.	2 or 3
9.	4 or 5 or 6 or 7
10.	1 and 8 and 9
11.	limit 10 to yr="1994 - 2013"

Note: Searches were performed using OvidSP, in which ".af." represents all fields, ".mp." represents multipurpose search, "exp" represents explode to include broader terms (e.g., dyspnea) and related terms (e.g., immunologic disorders), and "yr" represents year of publication.

Study selection and eligibility criteria

Study selection was conducted in two stages. Initially, the first author screened the titles and abstracts of all retrieved records to identify articles with relevant research objectives and methods and decide whether to obtain the full text. Subsequently, the full texts were independently assessed for eligibility by the first and second authors.

Eligibility criteria were defined by types of studies, participants, comparisons and outcome measures (Liberati et al., 2009). Only empirical quantitative studies that were published in peer-reviewed journals since the definition of QoL by the WHOQOL Group (1994-2013) and written in English were considered. Duplicate or secondary publications on the same sample were excluded to avoid multiple-publication bias. In such cases, priority was given to the article reporting data from the largest sample. For types of participants, criteria included samples of 7- to 18-year-old children and adolescents with clinical diagnoses of asthma or parents of children and adolescents with asthma. For types of comparisons, studies were required to report direct comparisons between children and adolescents with asthma or their parents and age-matched community/healthy controls. Finally, the primary outcome for this review was the mean difference (MD) between asthma and control groups on overall QoL for children and adolescents, either by self- or parent-report, and parents' overall QoL. Because QoL is multi-dimensional in nature and several QoL questionnaires provide a profile instead of a single index (Ravens-Sieberer et al., 2006), we considered the MD on QoL core domains (physical, emotional, social and school functioning) as secondary outcomes. For assessing pediatric QoL, both generic and disease-specific instruments were included, provided that they assessed QoL as a broad-ranging multi-dimensional construct, and not only health status, and were applicable, at least in part, to healthy children and adolescents. Following the recommendations of Braido and colleagues (2010) for QoL assessment in respiratory allergy, the studies were also required to use instruments that were psychometrically validated for the targeted age range and language/cultural context.

Inter-rater agreement on reasons for study exclusion was calculated with Cohen's Kappa coefficient, considering $k < .00$ as poor, $k \leq .20$ as slight, $k \leq .40$ as fair, $k \leq .60$ as moderate, $k \leq .80$ as substantial and $k > .81$ as almost perfect agreement (Landis & Koch, 1977). Disagreements were resolved by discussion to reach consensus.

Data extraction

A data collection form was developed for this review using the Data Extraction Template for Cochrane Reviews (The Cochrane Consumers and Communication Review Group, 2013) as a guide. Data were extracted by the first author and verified for accuracy by the second author. For each study, we extracted information on: publication information (i.e., authors, year and contact

information for the corresponding author); methods (i.e., study design, methods and settings for participant recruitment, and inclusion/exclusion criteria for participation in the study); participants (i.e., number of eligible and included participants, non-response rate, country of origin, age, sex and clinical characteristics, including asthma severity, medication and comorbidities with other health conditions); outcomes (i.e., conceptual definitions of primary and secondary outcomes adopted by the authors, methods and instruments used for assessing outcomes, and reliability and validity of outcome measures); and results for asthma and control groups (i.e., sample size, mean [*M*] and standard deviation [*SD*] for continuous outcome, subgroup analyses and controlled variables).

When summary data (*M*, *SD*) were not available for each group, other descriptive statistics (e.g., medians and interquartile ranges, standard errors or CI) or results from comparative analyses (e.g., *t* or *F* statistics) were extracted and converted into the desirable format (Higgins & Green, 2008; Hozo, Djulbegovic, & Hozo, 2005). For studies reporting data separately for subgroups of participants (e.g., children and adolescents; boys and girls), data were gathered into a single sample size that combined *M* and *SD* values (Higgins & Green, 2008). When data were not directly reported in the article and could not be computed from the available data, additional information was requested from the corresponding author by email. Data from the same study that was reported in multiple journal articles were extracted together.

Quality assessment

The methodological quality of individual studies included in the systematic review was independently assessed by the first and second authors, using an adapted version of the Newcastle-Ottawa Quality assessment scale (Wells et al., 2010). Studies were awarded up to 11 points based on selection of participants (maximum of 5 points), comparability between asthma cases and controls (maximum of 2 points) and QoL ascertainment (maximum of 4 points). Specifically for selection of participants, 1 point was allotted for adequate definition of cases (i.e., asthma diagnosis established by a physician based on medical records or physiological indicators), 1 point for representativeness of cases (i.e., selection of a random sample of patients, all eligible patients in a defined healthcare/educational institution or consecutive series of patients over a defined period of time), 1 point for adequate definition controls (i.e., healthy controls with no history of chronic health conditions), 1 point for selection of controls within the same community/geographic area as cases, and 1 point for response rate that was similar for cases and controls or higher than 80% for the total sample. Regarding comparability between asthma cases and controls, 1 point was allotted if the study controlled for children/adolescents' age and 1 point if the study controlled for any additional confounders. Finally, for ascertainment of QoL, 1 point was allotted for the use of age-appropriate measures that were psychometrically tested in the study sample and presented good psychometric

properties in terms of reliability and validity, 1 point for the use of patients' or parents' self-reported measures or 2 points for inclusion of both patients and parents, and 1 point for the use of the same procedures for assessing cases and controls. Studies awarded 0-3 points were considered to be low quality, 4-7 points were average quality and 8-11 points were high quality. Inter-rater agreement was calculated with Cohen's Kappa coefficient (Landis & Koch, 1977) and disagreements were resolved by discussion until consensus.

Data analyses

Meta-analyses for continuous data were performed with the Review Manager, Version 5.2. (The Cochrane Collaboration, 2012), using the inverse-variance random-effects method. Because this statistical method assumes that the outcomes have a normal distribution, skewness was inspected for both asthma and control groups in each study by checking whether the mean was smaller than twice the standard deviation (Altman & Bland, 1996).

Although QoL instruments often use different response scales, standardized scores ranging from 0 to 100 were the most widely used response scale across studies because they allow for comparisons between questionnaires and/or subscales with different numbers of items. Accordingly, we converted the *M* and *SD* values to the unit of the most commonly used scale for both asthma and control groups in each study. This approach enhances interpretability of summary estimates while preserving power and precision (Thorlund, Walter, Johnston, Furukawa, Guyatt, 2011). Once all results of individual studies were standardized, the MD between asthma and control groups and its associated 95% CI were computed for each outcome measure as the summary statistic for the estimate of effects.

Several covariates have been related to children/adolescents' and parents' QoL (e.g., socio-economic status) and they were likely to vary across studies; therefore, the random-effects model was chosen to incorporate between-studies heterogeneity. The τ^2 statistic (i.e., the squared estimated *SD* of underlying effects across studies) described between-studies variance and the I^2 index described the percent of variability in effect estimates due to heterogeneity (Borenstein, Hedges, Higgins, & Rothstein, 2009; Higgins, Thompson, Deeks, & Altman, 2003). When considerable heterogeneity was observed ($I^2 > 50\%$; Higgins et al., 2003), differences between subgroups of studies were examined to identify possible causes. To explore diversity in participants, we conducted subgroup analyses by age groups, considering participants aged 7-12 ears with a mean age ≤ 10 years as children and participants aged 11-18 years with a mean age ≥ 13 years as adolescents. To investigate methodological diversity, subgroup analyses comparing informants (self-*vs.* proxy-reports), type of controls (healthy *vs.* community controls), and quality ratings (high *vs.* moderate quality) were performed using χ^2-tests.

Results

Study selection

The literature search identified 3,887 non-duplicated articles, of which 272 articles were selected for full-text eligibility assessment (Figure 1). Two hundred and fifty two articles were excluded for the following reasons: absence of a sample of pediatric asthma patients/parents, or inclusion of a sample of pediatric patients/parents of patients with chronic health conditions including asthma, but no data reported separately for each condition (n = 54); the pediatric sample included children younger than 7 or older than 18 years and no data was reported for different age groups (n = 94); absence of community/healthy controls or use of normative data as a reference group (n = 77); no report of direct comparisons between asthma and control groups (n = 9); no data on children/adolescents' or parents' QoL as an outcome measure (n = 9); QoL definitions that were different from the one proposed by the WHOQOL Group (n = 4); qualitative research (n = 1); insufficient or inconsistent data (n = 3); and secondary publication on the same data and analyses (n = 1). Inter-rater agreement for exclusion reason was almost perfect, with k = .90 (p < .001).

Nineteen different studies reported in 20 journal articles met all inclusion criteria and were included in the systematic review.

Study characteristics

Of the 19 included studies, 17 (reported in 18 articles; Altiparmak, Altiparmak, & Sari, 2011; Covaciu, Bergström, Lind, Svartengren, & Kull, 2013; Danansuriya & Rajapaksa, 2012; French, Christie, & Sowden, 1994; French, Carroll, Christie, 1998; Grootenhuis, Koopman, Verrips, Vogels, & Last, 2007; Hallstrand, Curtis, Aitken, & Sullivan, 2003; Hutchings et al., 2007, 2008; Kojima et al., 2009; Matterne, Schmitt, Diepgen, & Apfelbacher, 2011; Merikallio, Mustalahti, Remes, Valovirta, & Kaila, 2005; Montalto, Bruzzese, Moskaleva, Higgins-D'Alessandro, & Webber, 2004; Moreira et al., 2013; Sawyer et al., 2001; Upton et al., 2005; Van Gent et al., 2007; Wang, Wang, Wang, Xu, & Zhang, 2012) examined the QoL of 32,874 children and adolescents and four studies (Gau et al., 2010; Hatzmann, Heymans, Ferrer-i-Carbonell, Van Praag, & Grootenhuis, 2008; Moreira et al., 2013; Van Gent et al., 2007) examined the QoL of 8,062 parents, from 13 different countries. The study design and sample characteristics are detailed in Table 2.

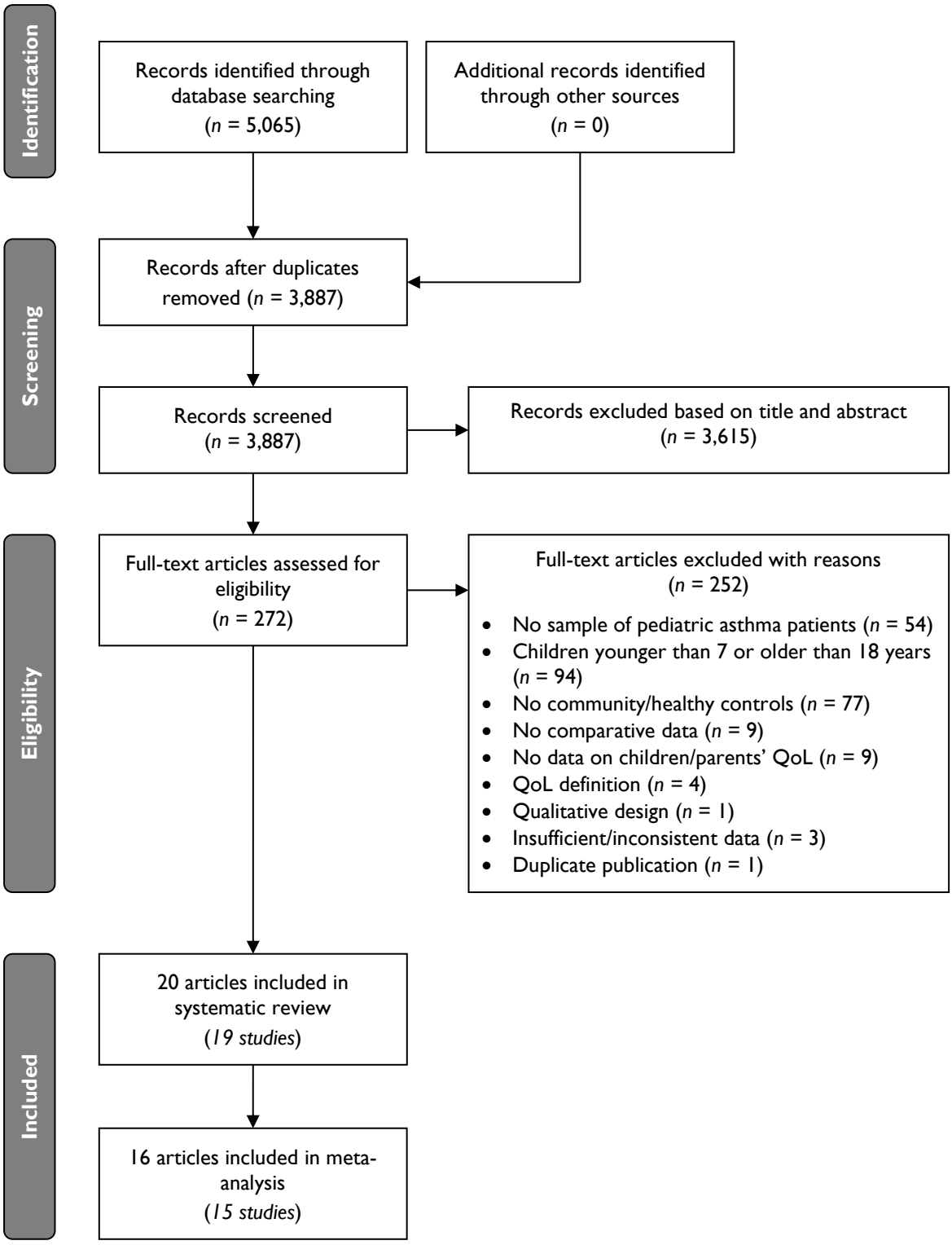

Figure 1 | Flowchart for selection of studies

Table 2 | Study design and sample characteristics reported in the 19 studies included in the systematic review

Authors, date of publication; country	*Study design; period of data collection*	*Selection criteria*	*Sample size*	*Age in years M ±SD; range*	*Sex (%) male*	*Outcome measures*	*Quality of life dimensions*
Altiparmak et al., 2011; Turkey	Cross-sectional March 2008 – June 2008	NR	Cases: 94 adolescents with asthma Controls: 669 adolescents without asthma diagnosed by a doctor	Total sample: 13.2±0.9 Range: 11-15	Total sample: 49.0%	Kiddo-KINDL (generic self-report measure)	Physical functioning*, Emotional functioning*, Self-esteem, Family, Friends/social functioning*, School functioning/everyday activities*, QoL overall score**
Covaciu et al., 2013; Sweden	Prospective (comparative data from the 8-year follow-up) 2002-2004	NR	Cases: 199 children with asthma Controls: 3,021 children without asthma	Range: 8 years	Total sample: 49.7%	EuroQoL-5D (generic proxy-report measure)	QoL overall score (visual analogue scale)**
Danansuriya et al., 2012; Sri Lanka	Cross-sectional February 2008 – April 2008	Cases and controls with comorbidities or lacking parental consent were excluded	Cases: 115 adolescents with asthma Controls: 142 healthy adolescents	Cases: 13.0± 0.9 Controls: 12.8±0.8 Range: 12-14	Cases: 56.5% Controls: 52.1%	PedsQL™ 4.0 Generic Core Scales (generic self-report measure)	Physical functioning*, Emotional functioning*, Social functioning*, School functioning*, QoL overall score**
French et al., 1994; UK	Longitudinal (comparative data reported for both time 1 and 2)	Cases and controls with other chronic illnesses were excluded	Cases: 103 children with asthma Controls: 153 healthy children	Cases: 9.8±NR Controls: 9.5±NR Range: 8-11	Cases: 54% Controls: 52%	CAQ-Form B (asthma-specific self-report measure)	Active quality of living/physical functioning*, Passive quality of living, Distress, Severity
French et al., 1998; Australia	Cross-sectional	NR	Cases: 115 children and 120 adolescents with asthma (total = 235) Controls: 221 children and 185 adolescents without asthma (total = 406)	Cases: 10.23±NR Controls: 10.17±NR Range: 7-16	Cases: 56.2% Controls: 49.8%	CAQ-Form B; CAQ-Form C (asthma-specific self-report measures)	Active quality of living/ physical functioning*, Passive quality of living (Form B)/ Teenage quality of living (Form C), Distress, Severity, Reactivity (Form C)

Gau et al., 2010; Taiwan	Cross-sectional December 2001 – May 2002 (cases); August 2001 – January 2002 (controls)	For cases, mothers who have children with chronic health conditions other than asthma and who discontinued their child's visits to the doctor were excluded; Selection criteria not reported for controls	Cases: 229 mothers of children with asthma Controls: 6,431 female participants from the community	Cases: 36.76±5.07 Controls: NR Range: 21-54	NA	WHOQOL-BREF (generic self-report measure)	Physical functioning*, Psychological functioning*, Social relationships*, Environment, Overall QoL**
Grootenhuis et al., 2007; The Netherlands	Cross-sectional (data from several ongoing studies)	Controls with a chronic disease were excluded	Cases: 32 children with asthma Controls: 913 healthy children	Range: 8-11	Cases: 66% Controls: NR	TACQoL (generic self-report measure)	Physical functioning*, Motor functioning, Autonomy, Cognitive/school functioning*, Social functioning*, Emotional functioning (positive and negative emotions combined)*
Hallstrand et al., 2003; U.S.A.	Cross-sectional	NR	Cases: 37 adolescents with asthma Controls: 123 adolescents with no prior diagnosis of asthma	Total sample: 14.0±1.8	Total sample: 53.8%	PedsQL™ 3.0 Generic Core Scales (generic self-report measure)	Physical functioning*, Emotional functioning*, Social functioning*, School functioning*, General well-being, QoL overall score**
Hatzmann et al., 2008; The Netherlands	Retrospective study (cross-sectional data for QoL) January 2006 - September 2007	Parents were included if they have a child between 1 and 19 years of age with a chronic illness diagnosed > 1 year (cases) or without chronic illnesses (controls), living at home, and were able to fill out the questionnaire in Dutch or English	Cases: 87 parents of children/ adolescents with asthma Controls: 425 parents of healthy children/ adolescents	Cases: 42.2±6.7 Controls: 43.7±5.5	Cases: 13.8% Controls: 16.7%	TAAQoL (generic self-report measure)	Physical functioning (gross and fine motor functioning, sleep, pain, daily activities and vitality combined)*, Sexuality, Emotional functioning (positive emotions, depressive emotions and aggressiveness combined)*, Social functioning*, Cognitive functioning

Hutchings et al., 2007, 2008; UK	Longitudinal (comparative data reported for time 1)	Cases and controls with learning difficulties or with first language other than English, and controls having a health problem or currently using healthcare resources were excluded	Cases: 56 children/ adolescents with asthma and 37 parents Controls: 563 healthy children/ adolescents and 296 parents	Range: 8-18	NR	MMQL-Youth and Parent Form (generic self- and proxy-report measures)	Physical functioning*, Appearance, Emotional functioning*, Social functioning*, School functioning*
Kojima et al., 2009; Japan	Cross-sectional May 2005 – June 2005	NR	Cases: 1,438 adolescents with asthma Controls: 10,740 adolescents without asthma	Range: 13-14	NR	Kiddo-KINDL (generic self-report measure)	Physical functioning*, Emotional functioning*, Self-esteem, Family cohesion, Friends/social functioning*, School functioning/everyday activities*, QoL overall score**
Matterne et al., 2011; Germany	Cross-sectional May 2003 – May 2006	NR	Cases: 263 adolescents with asthma Controls: 6,244 adolescents without asthma	Range: 11-17	Total sample: 51.0%	KINDL-R (generic self-report measure)	Physical functioning*, Emotional functioning*, Self-esteem, Family, Friends/social functioning*, School functioning/everyday activities*, QoL overall score**
Merikallio et al., 2005; Finland	Cross-sectional February 2001 – March 2001	Cases and controls were excluded due to missing parental consent or missing data	Cases: 192 adolescents with asthma Controls: 1,792 adolescents without asthma	Total sample: 13.2±1.4 Range: 11-15	Total sample: 45.6%	CHQ-Child form (generic self-report measure)	Physical functioning*, Role/social-physical*, General health**, Bodily pain and discomfort, Family activities, Role/social-emotional, Role/social-behavioral, Self-esteem, Mental health/emotional functioning*, Behavior, Family cohesion
Montalto et al., 2004; U.S.A.	Cross-sectional 1999/ 2000 school year	NR	Cases: 238 children with asthma Controls: 1,054 children without asthma	Total sample: 8.5±0.78 Range: 7-11	Cases: 53% Controls: 45%	KINDL (generic self-report measure)	Physical state*, Psychological well-being*, Social relationships*, Functional capacity in everyday life*, QoL overall score**

Moreira et al., 2013; Portugal	Cross-sectional January 2010 – June 2012	Cases and controls with comorbid chronic health conditions or developmental delay and lacking parental consent were excluded	Cases: 175 children and 133 adolescents with asthma (total = 308); 308 parents Controls: 171 healthy children and 128 healthy adolescents (total = 299); 299 parents	Cases: 12.24±2.64 for children; 41.27± 5.82 for parents Controls: 11.75±3.25 for children; 41.72± 5.54 for parents Range: 8-18	Cases: 63% of children; 14.3% of parents Controls: 46.2% of children; 9.0% of parents	KIDSCREEN-10 Index EUROHIS-QoL-8 Index (generic self-report measures)	QoL overall score (children/ adolescents)** QoL overall score (parents)**
Sawyer et al., 2001; Australia	Cross-sectional	NR	Cases: 236 children with asthma and 236 parents Controls: 251 community children and 1,625 parents	Cases: 10.4±1.1 Controls: 10.5±NR Range: 8-13	Cases: 55% Controls: 51%	CHQ-Child form and CHQ-Parent form (generic self- and proxy-report measures)	General health perceptions**, Physical activities*, Pain and discomfort, Self-esteem, Emotional functioning*, Behavioral problems, Role/social functioning-physical*, Role/social functioning-emotional, Role/social functioning-behavioral
Upton et al., 2005; UK	Cross-sectional	Controls with any chronic health problem were excluded	Cases: 99 children/ adolescents with asthma and 74 parents Controls: 1,034 healthy children/ adolescents and 665 parents	Total sample: 12.58±2.6 for self-reports; 11.86±2.3 for proxy-reports Range: 8-18	Total sample: 48.9% for self-reports; 47.3% for proxy-reports	PedsQL™ 4.0 Generic Core Scales (generic self- and proxy-report measures)	Physical functioning*, Emotional functioning*, Social functioning*, School functioning*, QoL overall score**
Van Gent et al., 2007; The Netherlands	Cross-sectional September 2002 – April 2005	Cases were excluded due to missing data, refusal to participate in bronchial challenge test, or inability to meet technical conditions; Healthy controls had no asthma diagnosis or symptoms in the last 12 months and no reversible airway obstruction	Cases: 81 children with asthma and 81 parents Controls: 202 healthy children and 202 parents	Cases: 9.4±0.8 Controls: 9.4±0.7 Range: 7-10	Cases: 58% Controls: 50%	PAQLQ PACQLQ (asthma-specific self-report measures)	Activity/physical functioning*, Emotions*, Symptom, QoL overall score** (children) Activity/physical functioning*, Emotions*, QoL overall score** (parents)

Wang et al., 2012; China	Cross-sectional June 2007 – December 2007	Cases and controls with other systemic or neurological disorders, IQ < 85 and those who refused to participate were excluded	Cases: 81 adolescents with asthma Controls: 87 healthy adolescents	Cases: 15.20±1.10 Controls: 15.20±1.09 Range: 14-18	Cases: 64.2% Controls: 56.3%	MOS-SF-36 (generic self-report measure)	Physical functioning*, Role-physical, Bodily pain, General health, Vitality, Social functioning*, Role-emotional, Mental health/emotional functioning*, Health transition, QoL overall score**

CAQ – Childhood Asthma Questionnaire; CHQ – Child Health Questionnaire; *M* – mean; MMQL – Minneapolis-Manchester Quality of Life instrument; MOS-SF-36 – Medical Outcomes Study - Short Form; NR – not reported; PACQLQ - Pediatric Asthma Caregiver's Quality of Life Questionnaire; PAQLQ – Pediatric Asthma Quality of Life Questionnaire; *SD* – standard deviation; TAAQoL – TNO-AZL Questionnaire for Adult's Health-related Quality of Life; TACQoL – TNO-AZL Children's Quality of Life questionnaire; WHOQOL-BREF – World Health Organization Quality of Life Assessment - Abbreviated version; ** Considered as a primary outcome for this meta-analytic review; * Considered as a secondary outcome for this meta-analytic review.

The 17 studies examining children's and adolescents' QoL included a total of 3,807 pediatric asthma patients aged 7-18 years (*M* = 11.37; *SD* = 2.37; 54.38% male) and 29,067 controls (mean age = 11.52, *SD* = 2.28; 49.55% male). Of these, six studies (35.3%) assessed children aged 7-12 years with a mean age ≤ 10 years and seven studies (41.2%) assessed adolescents aged 11-18 years with a mean age ≥ 13 years; the remaining four studies included broader age ranges, with two performing independent analyses for different age groups (French et al., 1998; Moreira et al., 2013). The four studies examining differences in parents' QoL sampled 705 parents of children and adolescents with asthma (85.82% female; mean age = 39.75, *SD* = 6.13) and 7,357 parents of community/healthy children and adolescents (86.46% female; mean age = 42.88, *SD* = 5.60).

The majority of studies had a cross-sectional design (*n* = 15, 78.9%); of the four studies with a longitudinal design, only one reported case-control comparisons for both assessment times (French et al., 1994; for consistency, only data from the first assessment was used in quantitative analyses). Several studies did not report asthma clinical characteristics and the few studies that presented comparative data separately for different clinical groups used heterogeneous criteria for clustering (e.g., wheezing attacks during the previous month [Merikallio et al., 2005]; dyspnea during exercise [Hallstrand et al., 2003; Kojima et al., 2009]; peak expiratory flow lower than 80% [Wang et al., 2012]). For comparative analyses, nine studies (47.4%) selected healthy controls with no history of chronic conditions, eight (42.1%) selected children and adolescents without asthma but did not describe their health status, and two (10.5%) used a community sample as controls.

For assessing children's and adolescents' QoL, all studies but one (Covaciu et al., 2013) used self-report measures and three studies (Hutchings et al., 2007, 2008; Sawyer et al., 2001; Upton et al., 2005) followed a multi-informant approach by also including proxy-reports from 347 parents of pediatric asthma patients and 2,586 parents of community/healthy children and adolescents. A variety of instruments were used across studies to measure children's and adolescents' QoL, including eight generic (the KINDL [Ravens-Sieberer & Bullinger, 1998; Eser et al., 2008], the PedsQL™ Generic Core Scales [Danansuriya & Rajapaksa, 2012; Upton et al., 2005; Varni, Seid, & Rode, 1999], the Child Health Questionnaire [Landgraf, Abetz, & Ware, 1996; Pelkonen et al., 2001], the Dutch TNO-AZL Children's Quality of Life questionnaire [Vogels, Verrips, & Koopman, 2000], the Portuguese version of the KIDSCREEN-10 Index [Matos, Gaspar, & Simões, 2012], the British version of the Minneapolis-Manchester Quality of Life instrument [Hutchings et al., 2007, 2008], the EuroQoL-5D [Rabin & de Charro, 2001] and the Chinese version of the Medical Outcomes Study SF-36 Health Survey [Li, Wang, & Shen, 2002]) and two asthma-specific questionnaires (the Childhood Asthma Questionnaire [French et al., 1994; French et al., 1998] and the Dutch version of the Pediatric Asthma Quality of Life Questionnaire [Raat et al., 2005]). Most questionnaires were age appropriate and specifically designed to assess children/adolescents' QoL, except for the EQ-5D and the SF-36. Even so, a child-friendly version of the EQ-5D, which introduced only slight language

modifications to the Swedish EQ-5D adult version, presented good feasibility and discriminant validity between Swedish children/adolescents with and without asthma and/or rhinitis (Burström, Svartengren, & Egmar, 2011). Similarly, the SF-36 was developed to be self-rated by persons 14 years of age and older (Ware & Sherbourne, 1992) and presented good psychometric properties for Chinese adolescents (Wang et al., 2012).

For parents' QoL assessment, three studies used generic instruments (the Taiwanese version of the WHOQOL-BREF [Yao, Chung, Yu, & Wang, 2002], the Portuguese version of the EUROHIS-QoL-8 Index [Pereira, Melo, Gameiro, & Canavarro, 2011] and the Dutch TNO-AZL Questionnaire for Adult's Health-related Quality of Life [Bruil, Fekkes, Vogels, & Verrips, 2004]) and one used an asthma-specific measure (the Pediatric Asthma Caregiver's Quality of Life Questionnaire [Juniper et al., 1996]), all four with well-established psychometric properties. Most studies (n = 15, 78.9%) used profile instruments measuring several QoL domains (usually physical, psychological, and social), while only two studies (10.5%) assessed QoL as a single index.

Methodological quality

Figure 2 illustrates the proportion of studies that met the quality criteria defined according to the Newcastle-Ottawa Quality assessment scale (Wells et al., 2010) adapted for this review. Overall, 15 studies (78.9%) were assessed as average quality (Altiparmak et al., 2011; Covaciu et al., 2013; Danansuriya & Rajapaksa, 2012; French et al., 1994; French, et al., 1998; Gau et al., 2010; Grootenhuis et al., 2007; Hallstrand et al., 2003; Hatzmann et al., 2008; Hutchings et al., 2007, 2008; Kojima et al., 2009; Montalto et al., 2004; Sawyer et al., 2001; Van Gent et al., 2007; Wang et al., 2012) and four studies (21.1%) as high quality (Matterne et al., 2011; Merikallio et al., 2005; Moreira et al., 2013; Upton et al., 2005). The main reasons for low quality scores were the use of nonrepresentative samples (e.g., convenience sampling methods, 57.9%), no description of controls' health status (57.9%), response rates lower than 80% or not reported (84.2%), and the use of different procedures/settings in the completion of QoL questionnaires (52.6%). A detailed description of quality assessment is presented in Supplementary Material, Table S1. Inter-rater agreement for quality assessment was moderate, with k = .49 (p < .001), and consensus was reached for all studies.

Additional quantitative data were directly requested from the authors for seven studies and summary statistics were obtained for three studies (Grootenhuis et al., 2007; Hatzmann et al., 2008; Moreira et al., 2013); the remaining four studies (French, et al., 1998; Hallstrand et al., 2003; Kojima et al., 2009; Wang et al., 2012) were excluded from quantitative analyses due to insufficient or inconsistent data.

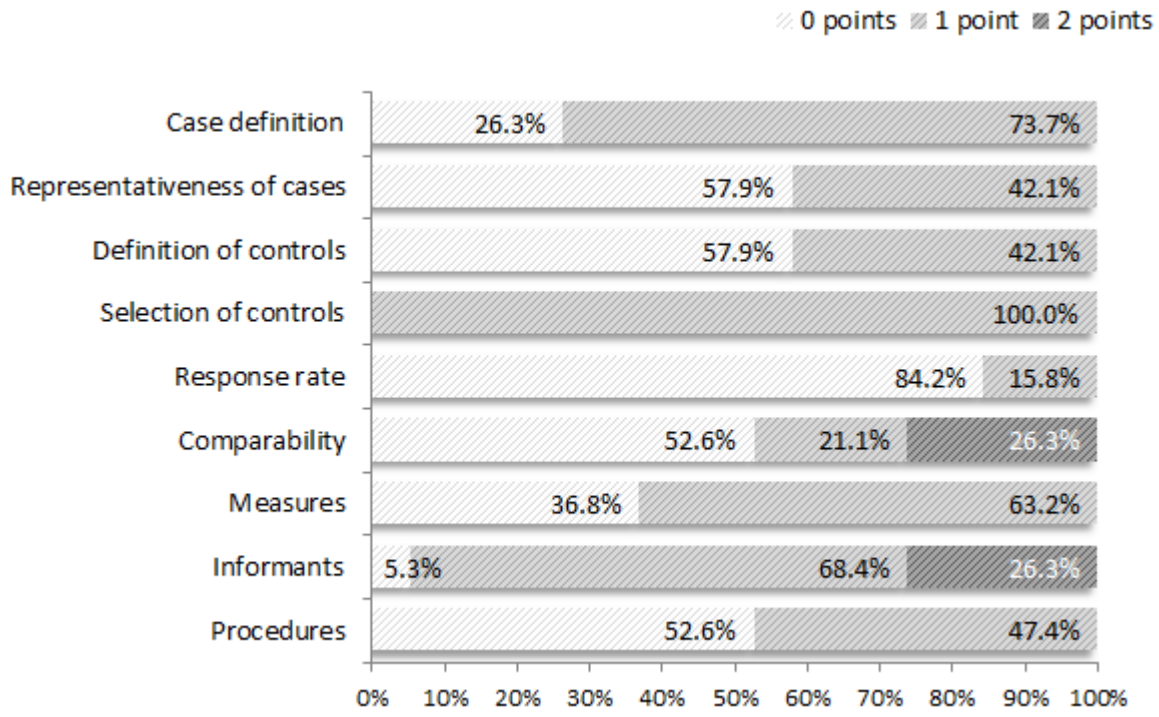

Figure 2 | Percentage of studies allotted with 0, 1 or 2 points according to the Newcastle-Ottawa Quality assessment scale adapted for the present study

Quality of life in children and adolescents with asthma

For quantitative synthesis of children's and adolescents' QoL outcomes, data were obtained from 13 studies comprising a total of 1,797 pediatric asthma patients and 13,266 controls, as well as 547 parents of children and adolescents with asthma and 5,607 parents of community/healthy children and adolescents as their proxies. The meta-analyses of the 10 studies presenting data for overall QoL (Figure 3.A) showed that children and adolescents with asthma had significantly lower QoL than their peers, with a MD of -7.48 (95% CI = -10.67/ -4.29, $p < .001$). Pooled estimates for each core domain of pediatric QoL confirmed a decreased physical (MD = -9.36, 95% CI = -11.85/ -6.86, $p < .001$; Figure 3.B), psychological (MD = -5.00, 95% CI = -7.17/ -2.82, $p < .001$; Figure 3.C) and social functioning (MD = -3.76, 95% CI = -5.80/ -1.72, $p < .001$; Figure 3.D) for pediatric asthma patients when compared to community/healthy controls. No significant differences were observed for school functioning (MD = -4.44, 95% CI = -9.23/ 0.35, $p = .07$; Figure 3.E). Between-studies variance indicated significant heterogeneity for all QoL domains, with I^2 ranging from 82 to 96%.

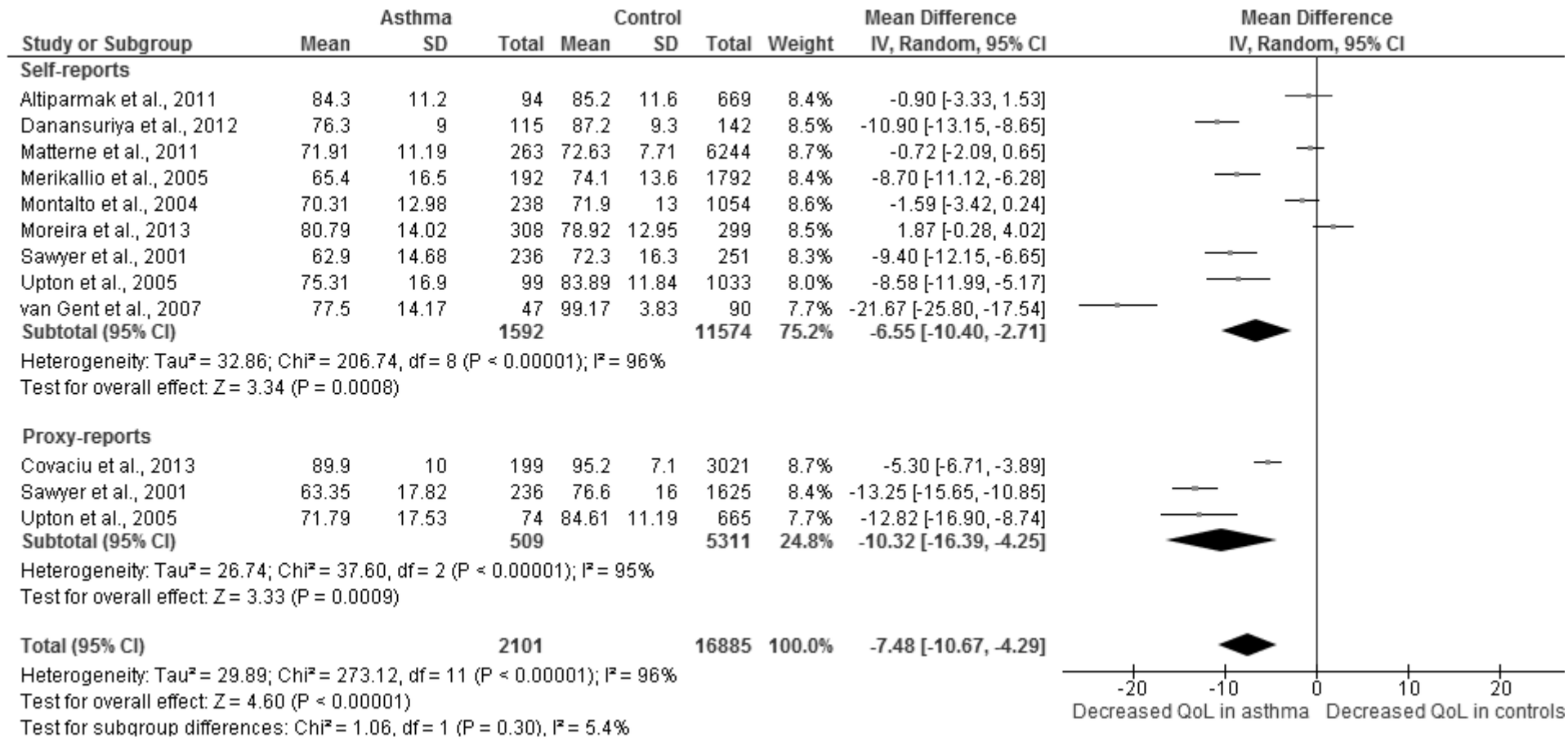

Figure 3.A | Forest plots for meta-analysis of differences in children/adolescents' overall QoL

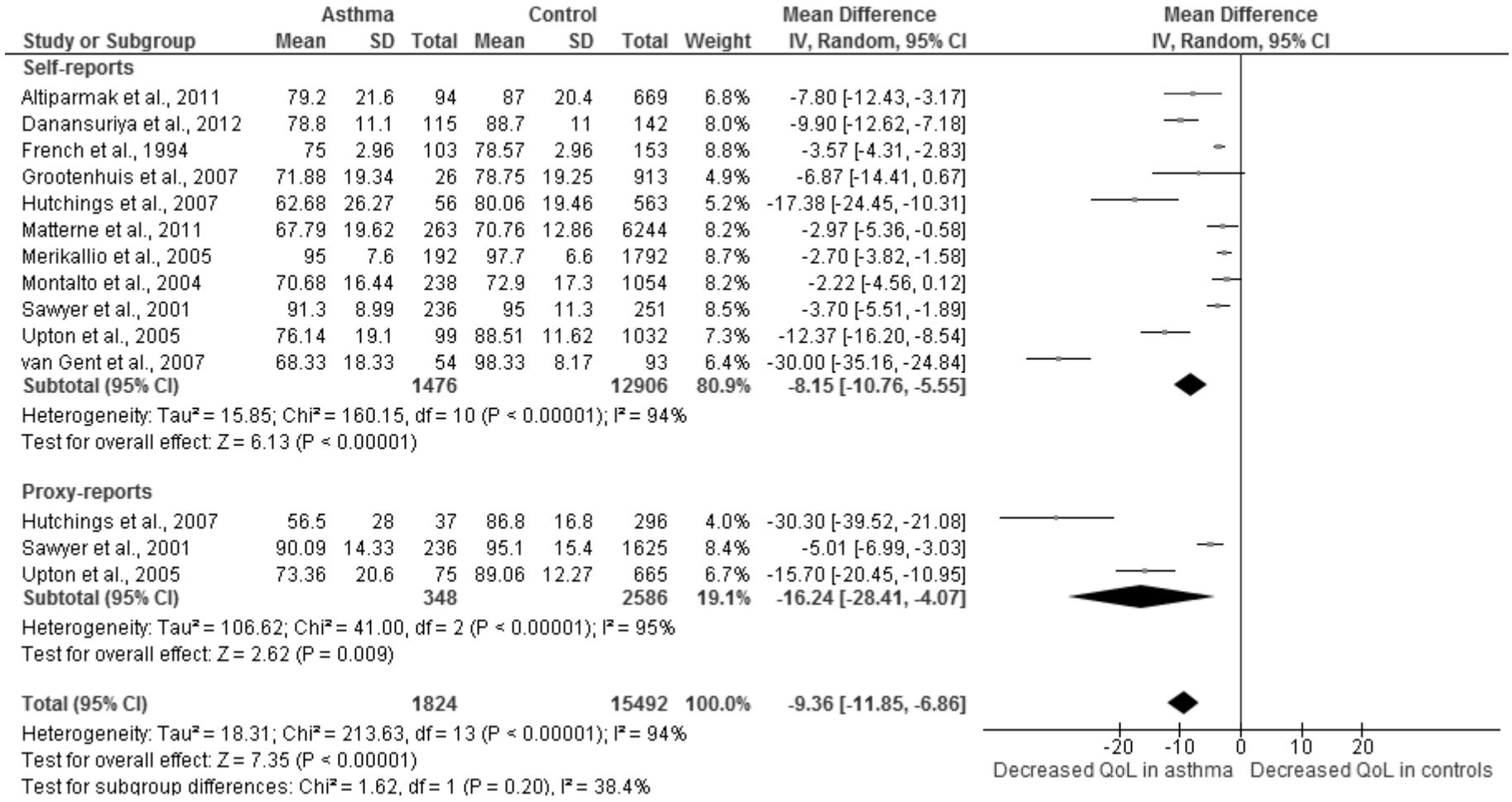

Figure 3.B | Forest plots for meta-analysis of differences in children/adolescents' physical functioning

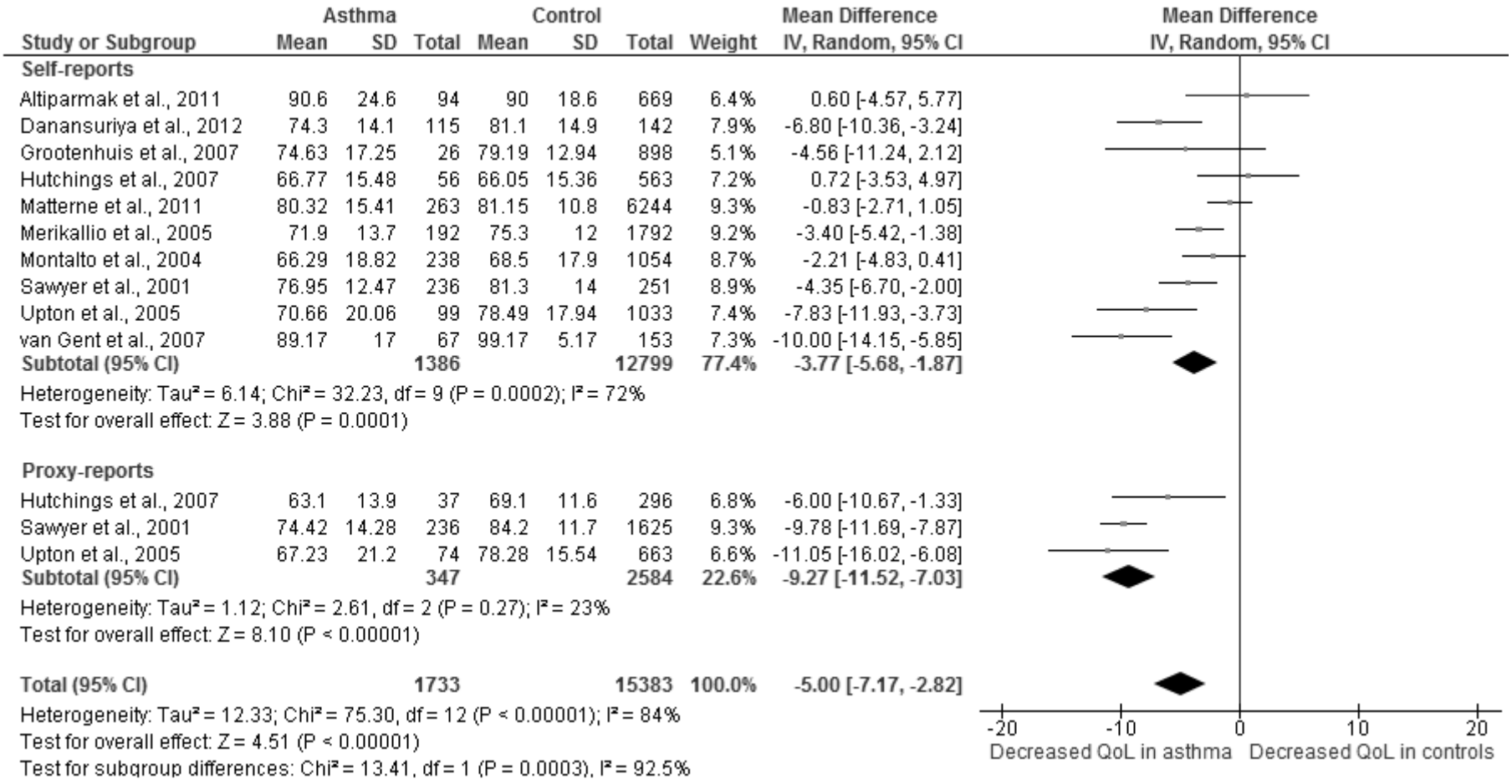

Figure 3.C | Forest plots for meta-analysis of differences in children/adolescents' psychological functioning

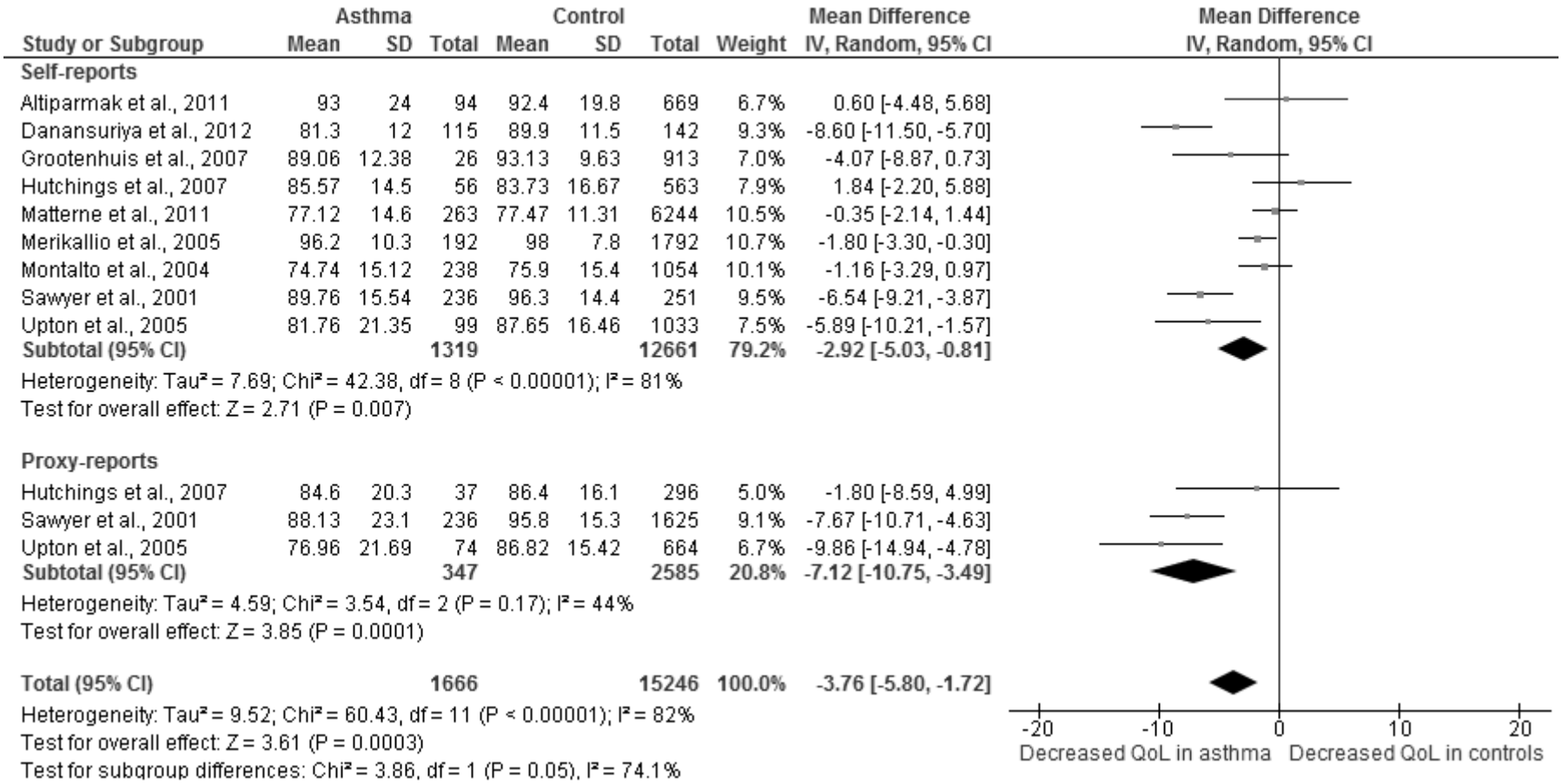

Figure 3.D | Forest plots for meta-analysis of differences in children/adolescents' social functioning

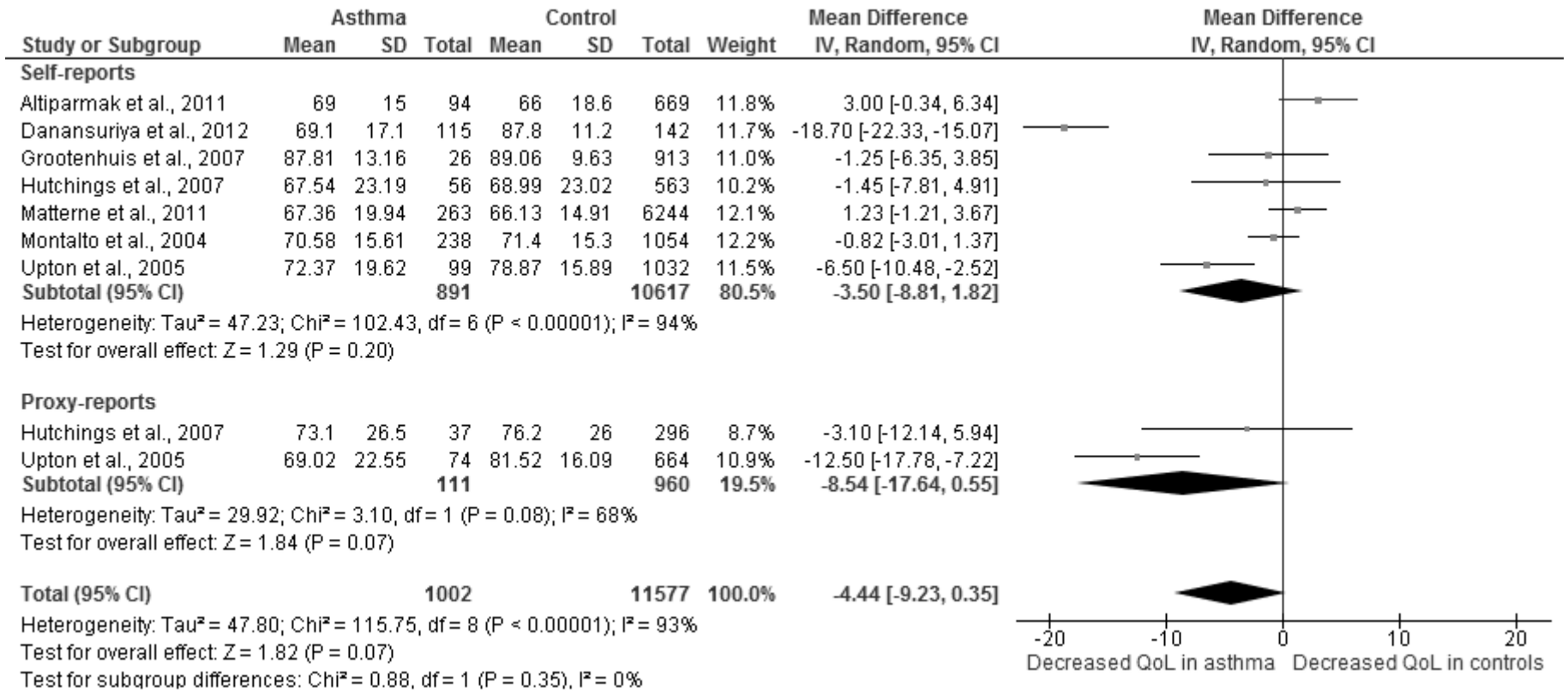

Figure 3.E | Forest plots for meta-analysis of differences in children/adolescents' school functioning

Quality of life in parents of pediatric asthma patients

Data on parents' QoL outcomes were obtained from a total of 666 parents of pediatric asthma patients and 7,328 parents of community/healthy children and adolescents that were reported in four studies. Of these, three studies presented data for overall QoL (Gau et al., 2010; Moreira et al., 2013; Van Gent et al., 2007), three examined physical and psychological functioning (Gau et al., 2010; Hatzmann et al., 2008; Van Gent et al., 2007) and two assessed social functioning (Gau et al., 2010; Hatzmann et al., 2008). The results from the meta-analysis (Figures 4.A, 4.B, 4.C and 4.D) showed that parents of pediatric asthma patients had significantly impaired physical functioning when compared to parents of community/healthy children and adolescents (MD = -10.15, 95% CI = -12.21/ -8.08, $p < .001$), with low heterogeneity across the three included studies (I^2 = 32%). Conversely, pooled estimates indicated no significant differences for parents' overall QoL (MD = -4.09, 95% CI = -9.35/ 1.17, $p = .13$), psychological functioning (MD = -6.60, 95% CI = -14.10/ 0.91, $p = .08$) or social functioning (MD = -1.84, 95% CI = -4.37/ 0.69, $p = .15$), but high heterogeneity across studies was observed for overall QoL (I^2 = 93%) and psychological functioning (I^2 = 94%).

Subgroup analyses

Table 3 presents the results for subgroup analyses by informant (self- *vs*. proxy-report), age group (children aged 7-12 years with a mean age ≤ 10 years *vs.* adolescents aged 11-18 years with a mean age ≥ 13 years), type of controls (healthy controls *vs.* community controls) and quality rating (high quality *vs.* medium quality) for children's and adolescents' QoL outcomes. The high heterogeneity across studies was explained by informants and controls' health status. Specifically, studies that relied on parent-reports presented significantly decreased children/adolescents' psychological and social functioning than studies based on patient-reported measures (Figures 3.C and 3.D). Moreover, greater impairments were found for physical, psychological, and school functioning of children and adolescents with asthma (although only marginally significant for the last two domains) when studies compared them to healthy controls with no history of chronic conditions, than when studies selected community children and adolescents without asthma as controls, without adjusting for the presence of other health conditions. No significant differences were observed between subgroups of studies according to age group or quality rating. The forest plots for subgroup differences are presented in Supplementary Material, Figures S1-S3.

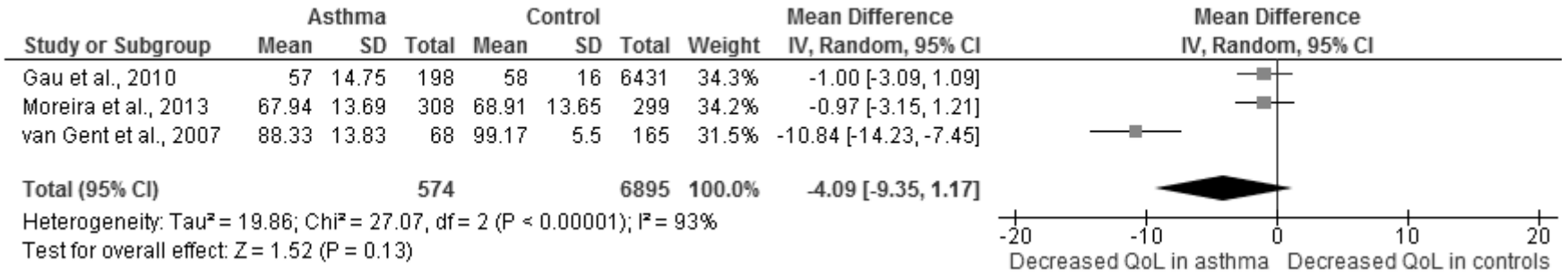

Figure 4.A | Forest plots for meta-analysis of differences in parents' overall QoL

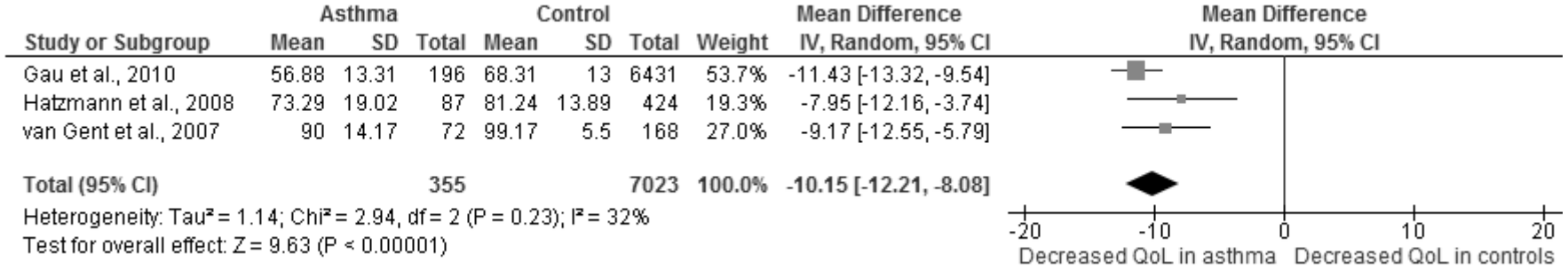

Figure 4.B | Forest plots for meta-analysis of differences in parents' physical functioning

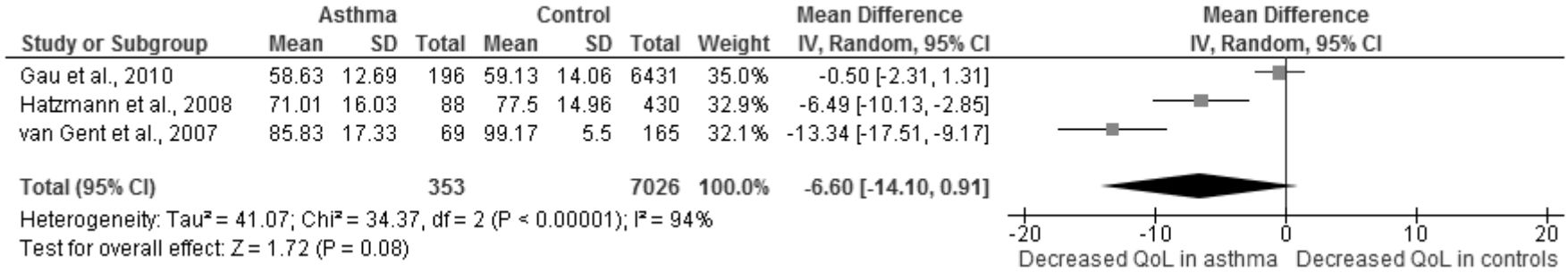

Figure 4.C | Forest plots for meta-analysis of differences in parents' psychological functioning

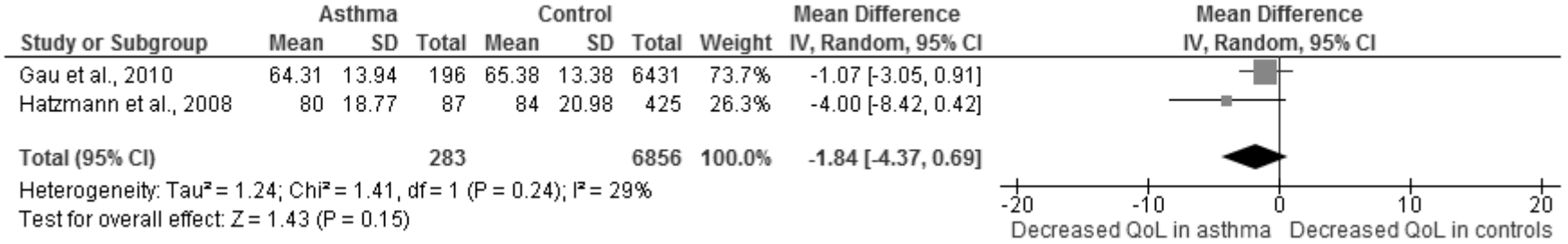

Figure 4.D | Forest plots for meta-analysis of differences in parents' social functioning

Table 3 | Children/adolescents' QoL according to subgroup analyses

	Informants		*Age group*		*Type of controls*		*Methodological quality*	
Outcome	Self-reports	Proxy-reports	Children	Adolescents	Healthy	Community	High	Average
Overall QoL								
Number of studies	9	3	3	5	4	5	4	5
MD	-6.55	-10.32	-7.76	-3.27	-9.72	-4.16	-3.91	-8.72
95% CI	[-10.40/ -2.71]	[-16.39/ -4.25]	[-17.85/ 2.33]	[-8.35/ 1.81]	[-18.78/ -0.65]	[-7.65/ -0.68]	[-8.75/ 0.93]	[-14.79/ -2.65]
χ^2	1.06		0.61		1.25		1.48	
Physical functioning								
Number of studies	11	3	4	4	6	5	3	8
MD	-8.15	-16.24	-10.38	-5.59	-13.20	-3.14	-5.63	-9.57
95% CI	[-10.76/ -5.55]	[-28.41/ -4.07]	[-18.26/ -2.50]	[-9.12/ -2.07]	[-20.22/ -6.17]	[-4.19/ -2.10]	[-10.07/ -1.19]	[-13.49/ -5.65]
χ^2	1.62		1.18		**7.70****		1.70	
Psychological functioning								
Number of studies	10	3	3	4	5	5	3	7
MD	-3.77	-9.27	-5.51	-2.73	-5.80	-2.40	-3.56	-3.88
95% CI	[-5.68/ -1.87]	[-11.52/ -7.03]	[-10.90/ -0.13]	[-5.38/ -0.09]	[-9.51/ -2.09]	[-3.93/ -0.87]	[-6.78/ -0.34]	[-6.47/ -1.30]
χ^2	**13.41****		0.82		**2.76**†		0.02	
Social functioning								
Number of studies	9	3	2	4	4	5	3	6
MD	-2.92	-7.12	-1.79	-2.66	-4.28	-1.98	-1.92	-3.18
95% CI	[-5.03/ -0.81]	[-10.75/ -3.49]	[-4.14/ 0.56]	[-6.02/ 0.71]	[-9.00/ 0.44]	[-4.01/ 0.04]	[-4.06/ 0.23]	[-6.52/ 0.16]
χ^2	**3.86***		0.17		0.77		0.39	
School functioning								
Number of studies	7	2	2	3	4	3	2	5
MD	-3.50	-8.54	-0.89	-4.78	-7.16	0.86	-2.47	-3.88
95% CI	[-8.81/ 1.82]	[-17.64/ 0.55]	[-2.90/ 1.12]	[-17.19/ 7.63]	[-15.86/ 1.54]	[-1.22/ 2.95]	[-10.04/ 5.10]	[-11.62/ 3.86]
χ^2	0.88		0.37		**3.09**†		0.07	

CI – confidence interval; MD – mean difference

** $p \leq .01$; * $p \leq .05$; † $p \leq .10$

Discussion

Summary of evidence

This is the first meta-analytic review to gather comparative studies of QoL outcomes between pediatric asthma patients or their parents and community/healthy controls. The results from the meta-analyses showed that children and adolescents with asthma are at a greater risk for decreased QoL than their peers without asthma, particularly in physical, psychological, and social domains. Parents of children and adolescents with asthma also presented diminished QoL, but only in the physical domain. These results were strengthened by the ascertainment of type of informant (self- or proxy-reports) and controls' health status as methodological features explaining the heterogeneous results across studies.

The deleterious effect of asthma on children's and adolescents' QoL is consistent with previous research on other psychosocial adaptation outcomes. A previous meta-analysis on behavioral adjustment described a higher risk for internalizing and externalizing problems among pediatric asthma patients compared to healthy controls or normative data (McQuaid, Kopel, & Nassau, 2001). However, the broad CI associated with differences in QoL mean scores between asthma and control groups that were found in most studies included in this meta-analysis reveal considerable within-studies variability, which suggests that children and adolescents with asthma may experience different levels of QoL impairments.

Pooled results also showed high between-studies heterogeneity, which was partially explained by the informant of pediatric QoL. A major trend for using self-report measures was observed; however, studies that relied on parent-reports as proxies identified larger impairments in children's and adolescents' psychological and social functioning than studies that used self-report measures. A previous systematic review on parent-child agreement in the context of pediatric chronic conditions had shown that parents were more likely to underrate pediatric QoL than children and adolescents themselves, with lower levels of agreement for non-observable domains, such as emotional or social QoL (Eiser & Morse, 2001). On the one hand, these findings may reflect a bias resulting from parents' expectations and concerns; on the other hand, parents may be more reliable in detecting psychosocial problems associated with pediatric asthma – the so-called "hidden morbidities" (Varni, Burwinkle, & Lane, 2005).

Between-studies heterogeneity was also explained by controls' health status as there were greater differences on physical, psychological and school functioning in studies that compared pediatric asthma patients to healthy controls than in studies that selected community children and adolescents without asthma as controls. Over recent years, technological advances in medicine have resulted in increased survival rates and greater prevalence of chronic conditions in childhood and

adolescence (Varni, Limbers, & Burwinkle, 2007). Consequently, community samples are likely to include a number of children and adolescents with other chronic conditions and QoL impairments, which may bring the QoL scores of community and asthma groups closer, thus leading to a lower magnitude of differences.

For parents' QoL, the existing studies are too scarce to draw robust conclusions. However, the few included studies consistently reported decreased physical functioning among parents of children and adolescents with asthma in comparison to parents of community/healthy children and adolescents. On the one hand, the decreased physical functioning may reflect asthma morbidity in the parents since asthma has a heritable component with an overall prevalence above 13% in the first-degree relatives of pediatric asthma patients (Sibbald, Horn, Brain, & Gregg, 1980). On the other hand, the burden of caring for a child with asthma may affect parents' everyday life and functioning, particularly in terms of lower quantity and quality of sleep, greater daytime fatigue, and poorer work attendance and productivity (Fiese, Winter, Anbar, Howell, & Poltrock, 2008; Raina et al., 2004). Conversely, no significant differences were found for psychological and social domains, but high levels of between-studies heterogeneity were observed.

Limitations

Some limitations at the individual study and review levels should be acknowledged. First, diverse QoL measures were used across studies, resulting in a dissimilar methodological operationalization of the QoL construct in terms of number and content of items and response scales. Moreover, the minimally important difference, i.e., the smallest difference/change in an outcome measure perceived, on average, as beneficial by the patients (Guyatt, Osoba, Wu, Wyrwich, & Norman, 2002) was not established for the great majority of QoL measures. Even if a half standard deviation has been acknowledged as a "universal" threshold of discrimination for differences/changes in health-related QoL (Norman, Sloan, & Wyrwich, 2003), the minimally important difference is likely to vary across clinical and demographic characteristics of the sample and across instruments with dissimilar measurement properties (e.g., different number of items, floor and ceiling effects, etc.; Thorlund et al., 2011). In this meta-analytic review, variability in outcome measures was addressed by performing distinct meta-analyses for QoL total scores and each domain of functioning and converting response scales into standardized scores to allow comparability across QoL domains. Future research should translate and adapt the existing reliable and valid measures to facilitate cross-cultural comparisons and determine the minimally important difference for patient-reported outcomes to enhance interpretability in both clinical trials and meta-analyses.

Second, our results should be interpreted with caution due to high levels of between-studies

heterogeneity. Participant and methodological diversity was addressed by using random-effects models and subgroup analyses by informant, age group, type of controls and quality rating. However, because of the different criteria for clustering asthma clinical groups that were used across studies, we were unable to explore asthma severity and control levels as potential factors explaining heterogeneity. Additionally, despite the high heterogeneity observed for parents' overall QoL and psychological functioning, subgroup analyses could not be performed because at least one of the subgroups would have only one study.

Finally, our literature search was restricted to English-language articles and the "grey literature" was not considered, which may have introduced publication bias. However, the small number of studies included in each meta-analysis limited the use of tests for detecting funnel plots asymmetry because they have low power to distinguish chance from real asymmetry when there are less than 10 studies (Egger, Davey Smith, Schneider, & Minder, 1997; Higgins & Green, 2008).

Implications for research and clinical practice

The ascertainment of the magnitude of QoL impairments and the identification of the most affected QoL domains among children and adolescents with asthma and their parents, in comparison to community/healthy controls, has important implications for research and clinical practice. First, the QoL of pediatric asthma patients and their parents should be routinely assessed in pediatric healthcare services and included as a broad-ranging outcome in clinical trials. For assessing pediatric QoL, our findings reiterate the need to include self- and parent-reports as complementary sources of information and the importance of selecting reliable and valid, age-appropriate and cross-culturally comparable measures. Even if single-index measures may be attractive as screening tools in clinical and research contexts due to their small number of items, our results suggest that profile measures covering physical, psychological and social functioning may be more sensitive in detecting the most impaired areas of patients' and parents' QoL.

Second, further case-control studies on QoL outcomes are required in the pediatric asthma context, especially for parents' QoL. Future comparative research should carefully select healthy controls and avoid using community samples or normative data, and also adjust for potential clinical and socio-demographic confounders. Moreover, it is urgent to disseminate valid procedures for assessing asthma clinical characteristics that can be used worldwide, such as the Global Initiative for Asthma guidelines (GINA, 2008), to enable cross-cultural comparisons by asthma severity and control levels.

Third, research can now move from merely descriptive and comparative studies to the examination of adaptation processes explaining within-studies heterogeneity. Addressing the complex interactions between disease-related risks and resistance factors, namely, family functioning,

social support and coping strategies, may contribute to explain the variability in children/adolescents' and parents' QoL outcomes (Wallander, Pitt, & Mellins, 1990; Wallander, Varni, Babani, Banis, & Wilcox, 1989).

Finally, the identification of specific domains of decreased functioning can assist healthcare providers to cost-effectively allocate resources, define appropriate goals for multidisciplinary interventions and evaluate its effectiveness. Preliminary evidence for the efficacy of psychosocial interventions in children/adolescents with asthma (e.g., cognitive-behavioral therapies, relaxation techniques, supportive counseling), in addition to pharmacological treatments, was found for a variety of adaptation outcomes (Yorke, Fleming, & Shuldham, 2005). Psychosocial interventions in pediatric settings should also aim to reduce the parental burden of caring for a child with asthma and improve physical well-being. Family functioning, social support and coping strategies (Wallander et al., 1989; Wallander et al., 1990) are specific intervention targets that can moderate the impact of asthma on children/adolescents' and their parents' QoL outcomes.

Conclusion

Over the past couple of decades, a number of descriptive studies have been conducted to characterize the QoL outcomes of pediatric asthma patients, in comparison to healthy or community children and adolescents. Current evidence, as based on a meta-analysis of those results, indicates that children and adolescents with asthma are at a greater risk for impairments in overall QoL and present lower levels of physical, psychological and social functioning, in comparison to community/healthy controls. Complementarily, a synthesis of results observed in studies addressing the assessment of QoL outcomes in parents who have children with asthma points to a more impaired QoL in the physical domain, which generally encompasses those facets related to sleep, fatigue and work attendance/productivity, in comparison to controls. QoL outcomes research conducted in the context of pediatric asthma has been marked by a preferred use of self-reported measures; however, larger QoL impairments tend to be observed in studies that employed proxy-report measures. Pediatric QoL differences also tend to be larger in comparative studies that used healthy controls instead of general community controls. Taken altogether, these results illustrate the decisive need of incorporating a parent-child perspective in assessment and intervention processes targeting the QoL of pediatric patients with asthma.

Research conducted over the past 20 years on the QoL of children with asthma and their parents enabled the ascertainment of QoL impairments for this pediatric group. The challenge is now to move from outcomes description to QoL outcomes prediction. In this line of thought, the research on QoL in pediatric asthma is expected to flourish in the years to come, with an increased number of studies examining bio-psycho-social mediating pathways for QoL outcomes, while

incorporating a dyadic parent-child perspective in their designs. To improve their clinical and ecological validity, those studies must increase their methodological complexity by optimally including multiple informants, examining individual and family levels of analysis, and crossing biological and psychosocial variables. Hopefully, a greater substantiation of a parent-child perspective in QoL research for pediatric asthma will result in a greater number of studies simultaneously employing self- and proxy-reports and linking the children's and their parents' adaptation processes and outcomes.

Key issues

- The large amount of papers on quality of life (QoL) of children/adolescents with asthma and/or their parents that were published in the past 20 years illustrates the growing importance of QoL as an essential endpoint in pediatric research and healthcare contexts.
- Children and adolescents with asthma are at a greater risk for decreased QoL, in general, and physical, psychological and social functioning, in particular, compared to their peers without asthma.
- A major trend for using self-report QoL measures was observed across studies; however, patient- and parent-reports provide different but complementary data, and thus a multi-informant approach to pediatric QoL assessment is recommended.
- Over the past two decades, there has been a proliferation of instruments specifically designed for QoL assessment in children and adolescents, resulting in a dissimilar methodological operationalization of the QoL construct and hindering cross-cultural comparisons.
- Apart from the type of informants and the health status of controls, the severity of the underlying disease and responsiveness to treatments may contribute to explain the high levels of between-studies heterogeneity; however, the different criteria that were used across studies for clustering asthma clinical groups prevented the examination of clinical variables in this meta-analysis.
- The QoL of parents of children/adolescents with asthma has been understudied; still, the few studies examining their QoL in relation to parents of healthy children consistently indicate QoL impairments in the physical domain.
- The ascertainment of the magnitude of QoL impairments and the identification of the most affected QoL domains among pediatric asthma patients and their parents may contribute to outline realistic goals for medical treatments and psychosocial interventions and to evaluate its cost-effectiveness.

- Research can now move from descriptive studies to the examination of risk and resistance factors underpinning the adaptation processes to explain the within-study variability in children/adolescents' and their parents' QoL outcomes.

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Supplementary Material

Table S1 | Quality ratings for the 19 studies included in the systematic review using an adapted version of the Newcastle-Ottawa Quality assessment scale

Study	*Selection of participants* [a]					*Comparability* [b]	*Ascertainment of QoL* [c]			*Overall quality rating* [d]
	Case definition	Representativeness	Definition of controls	Selection of controls	Response rate		Measures	Informants	Procedures	
Altiparmak et al., 2011	Asthma diagnosed by a doctor ★	Stratified random + cluster sampling methods ★	NR	Community controls, within the same schools as cases ★	NR	No control for confounding variables	Kiddo-KINDL (Cronbach's α for the Turkish version: .78) ★	Adolescents ★	Same procedures for assessment of cases and controls ★	6 (average)
Covaciu et al., 2013	Asthma defined as 4 episodes of wheeze or at least 1 episode of wheeze in combination with prescribed inhaled steroids in the last 12 months ★	NR	NR	Community controls, with-in the same community as cases ★	84% (total sample at the 8-year follow-up) ★	The study controls for hereditary for allergy, sex, being a first born child and having a young mother ★	EuroQoL-5D (psychometric properties not reported for the Swedish children)	Parents	Same procedures for assessment of cases and controls ★	5 (average)
Danansuriya et al., 2012	Asthma diagnosis made by a physician ★	Consecutive cases from 4 hospitals selected on convenience basis ★	Healthy controls, with no physical or mental disabilities, chronic conditions or acute severe illness ★	Community controls randomly selected from schools ★	91.1% (control group)	No control for confounding variables	PedsQL™ 4.0 Generic Core Scales (Cronbach's α for the Sinhala version: .85) ★	Adolescents ★	Cases were assessed at the clinics in the presence of researchers; controls were assessed at classroom	6 (average)

French et al., 1994	Current diagnosis of asthma and/or recent prescription for asthma medication ★	NR	Healthy controls, with no chronic illnesses ★	Community controls from the same schools as 20% of cases ★	72% (test-retest for cases)	No control for confounding variables	CAQ-Form B (Cronbach's α between .44 and .82 for cases and between .21 and .69 for controls)	Children ★	80% of the cases were contacted through their doctor and assessed at home; 20% of the cases and controls completed questionnaires at classroom, supervised by 2 researchers	4 (average)
French et al., 1998	Asthma diagnosis based on medical (64%) or school records (36%) ★	NR	Community controls without asthma (other comorbidities not reported)	Community controls from the same schools as 36% of cases ★	32% for cases recruited at the Asthma Foundation of Western Australia; 79% for the school sample	No control for confounding variables	CAQ-Form B (Cronbach's α between .62 and .76); CAQ-Form C (Cronbach's α between .71 and .76) ★	Children ★	Cases recruited from the Asthma Foundation received and returned the questionnaires by post; the school sample was assessed in classrooms under the supervision of a researcher	4 (average)
Gau et al., 2010	Asthma cases referred by a pediatric immunologist ★	Convenience sample	NR	Female participants aged 21-54 years from the nationwide Taiwan community ★	95.4% (cases); 93.8% (controls) ★	No control for confounding variables	WHOQOL-BREF (Cronbach's α between .53 and .86 for cases and between .68 and .76 for controls) ★	Parents ★	Cases completed the questionnaires during a schedule clinical visit; Data collection method for controls was not described	5 (average)

Grootenhuis et al., 2007	NR	Cases selected by convenience at 2 healthcare institutions	Healthy controls, with no history of chronic disease ★	Dutch school-going children aged 8-11 years (data from the original TACQoL study) ★	NR	No control for confounding variables	TACQoL (Cronbach's α values in the original Dutch study ranged from .60 to .90) ★	Children ★	Patients completed the questionnaires in the waiting room of the outpatient clinic; Data collection method for controls was not described	4 (average)
Hallstrand et al., 2003	Asthma diagnosis based on interviews, self-report questionnaires and exercise challenge tests followed by spirometry ★	NR	Controls with no prior diagnosis of asthma	Adolescent athletes from the same three suburban western Washington schools as cases ★	62.5% (total sample; non-responden ts were described)	No control for confounding variables	PedsQL™ 3.0 Generic Core Scales (Cronbach's α for the core items in the original study: .83) ★	Adolescents ★	Same procedures for assessment of cases and controls ★	5 (average)
Hatzmann et al., 2008	NR	NR	Parents of children/ adolescents with no chronic illnesses ★	Controls recruited from schools in the same geographic area as cases ★	91.9% (total sample) ★	Cases and controls were comparable with regard parents' age, sex, marital status, educational level, and number of children ★	TAAQoL (Cronbach's α value in this study ranged from .60 to .96) ★	Parents ★	Same procedures for assessment of cases and controls ★	7 (average)

Hutchings et al., 2007, 2008	Asthma diagnosis made by a clinician according to the British Thoracic Society ★	NR	Healthy children/ adolescents without health problems and not currently using healthcare resources ★	Convenience sample recruited from local schools ★	64.2% (total sample)	No control for confounding variables	MMQL- Youth Form (Cronbach's α values between .72 and .90) MMQL- Parent Form (Cronbach's α values between .75 and .93) ★	Children/ adolescents and parents ★★	Cases completed the questionnaires either in clinic or at home; controls completed the questionnaires in the classroom under the supervision of a researcher	6 (average)
Kojima et al., 2009	Asthma diagnosis based on self-report questions	Random sample of 10% of the total population of adolescents in the 8th grade ★	NR	Community controls from the same randomly selected schools as cases ★	64.0% (total sample)	No control for confounding variables	Kiddo-KINDL (psychometric properties for the Japanese version not reported)	Adolescents ★	Same procedures for assessment of cases and controls ★	4 (average)
Matterne et al., 2011	Asthma was defined based on parents' reports of a medical diagnosis in the last 12 months ★	Representative sample of children and adolescents in 167 communities in Germany (data from the KiGGS study) ★	NR	Representative sample of children and adolescents in the same communities as cases ★	66.6% (total sample)	The study controls for age, sex, country of origin, SES, weight, and presence of mental health problems ★★	KINDL-R (Cronbach's α in the original psychometric study was .82 for the total score and ranged from .53 to .72 for sub-scales) ★	Adolescents ★	Same procedures for assessment of cases and controls ★	8 (high)

Merikallio et al., 2005	Parent's reports of asthma diagnosed by a doctor ★	Cases recruited from 175 randomly selected school classes ★	Controls with no history of wheezing attacks or asthma diagnosis	Controls recruited from the same randomly selected school classes as cases ★	60% (total sample)	The study controls for age, sex, geographical area, SES, family size, death/ divorce in the family, smoking of the child and presence of other serious illnesses of the child ★★	CHQ-Child form (Cronbach's α for the Finish version was .94 for the total score and ranged from .65 to .84 for domains) ★	Adolescents ★	Same procedures for assessment of cases and controls ★	8 (high)
Montalto et al., 2004	Asthma diagnosis based on parent-report questionnaire	All 3rd and 4th grade students attending 6 elementary schools ★	NR	Controls recruited from the same schools as cases ★	72% (total sample)	The study controls for sex and ethnicity ★	KINDL (psychometric properties for the modified version used in this study were not reported)	Children ★	Same procedures for assessment of cases and controls (both cases and controls completed the survey in school) ★	5 (average)
Moreira et al., 2013	Asthma diagnosis made by a physician ★	Convenience sample recruited in 3 healthcare institutions	Controls with no history of chronic health conditions or developmental delay ★	Controls recruited in 2 regular schools in the same geographic area as cases ★	NR	The study controls for age and sex ★★	KIDSCREEN-10 Index (Cronbach's α value in this study was .77) EUROHIS-QoL-8 Index (Cronbach's α value was .83) ★	Children/ adolescents and parents ★★	Cases completed the questionnaires in the health, supervised by a researcher; controls completed the questionnaires in the classroom	8 (high)

Sawyer et al., 2001	Asthma diagnosis based on parent-report questionnaire	Random sample of 59 schools ★	NR	Controls randomly selected across Australia (sample from the National Child and Adolescent Mental Health Survey) ★	79% (for cases)	No control for confounding variables	CHQ-Child form and CHQ-Parent form (psychometric properties in this study were not reported)	Children and parents ★★	Cases completed the questionnaires during home visits; Data collection method for controls was not described	4 (average)
Upton et al., 2005	Cases were identified based on medical records ★	NR	Healthy controls with no chronic health problems ★	Healthy controls recruited from 23 schools in South Wales ★	58.97% for cases; 74.77% for controls	The study controls for age and sex ★★	PedsQL™ 4.0 Generic Core Scales (Cronbach's α values exceeded .70 for all self- and proxy-report sub-scales and .90 for the total score) ★	Children/ adolescents and parents ★★	Cases completed the questionnaires either in clinic or at home under the supervision of a researcher; controls completed the questionnaires in class, under the supervision of a researcher	8 (high)
Van Gent et al., 2007	Asthma diagnosis based on parents' reports of physician-diagnosed asthma in the last 12 months ★	All eligible cases in 41 primary schools ★	Healthy controls with no asthma diagnosis or symptoms in the last 12 months and no reversible airway obstruction	Controls were randomly selected from the same schools as cases ★	64% (total sample)	The study controls for body weight ★	PAQLQ PACQLQ (psychometric properties in this study were not reported)	Children and parents ★★	Same procedures for assessment of cases and controls ★	7 (average)

Wang et al., 2012	Asthma diagnosis based on Global Initiative for Asthma (2005) and peak expiratory flow (PEF) ★	NR	Healthy controls without any severe progressive neurological diseases or systemic disorders ★	Controls were selected from the same outpatient units as cases ★	NR	No significant differences on sex, age, education level or family size were found between cases and controls ★★	MOS-SF-36 (psychometric properties not reported for the asthma group)	Adolescents ★	NR	6 (average)

CAQ – Childhood Asthma Questionnaire; CHQ – Child Health Questionnaire; MMQL – Minneapolis-Manchester Quality of Life instrument; MOS-SF-36 – Medical Outcomes Study-Short Form; NR – not reported; PACQLQ - Pediatric Asthma Caregiver's Quality of Life Questionnaire; PAQLQ – Pediatric Asthma Quality of Life Questionnaire; SES – Socio-economic status; TAAQoL – TNO-AZL Questionnaire for Adult's HrQoL; TACQoL – TNO-AZL Children's Quality of Life questionnaire; WHOQOL-BREF – World Health Organization Quality of Life Assessment - Abbreviated version; ★ = 1 point

[a] For selection of participants, 1 point was allotted for adequate definition of cases (i.e., asthma diagnosis established by a physician, based on medical records or physiological indicators), 1 point if the study reports on a random sample of patients, all eligible patients in a defined healthcare/educational institution or consecutive series of patients over a defined period of time, 1 point for adequate definition of healthy controls with no history of chronic health conditions, 1 point for selection of controls within the same community/geographic area as cases, and 1 point if the response rate was similar for cases and controls or > 80% for the total sample. [b] For comparability, 1 point was allotted if the study controls for children/adolescents' age, and 1 point if the study controls for any additional confounders. [c] For ascertainment of quality of life, 1 point was allotted for use of reliable, valid and age-appropriate measures, 1 point for use of patients' or parents' self-reported outcomes or 2 for inclusion of both patients and parents, and 1 point for use of the same method of ascertainment for cases and controls. [d] Studies can be awarded a maximum of 11 points: 0-3 points = low quality; 4-7 points = average quality; 8-11 points = high quality.

Supplementary Material

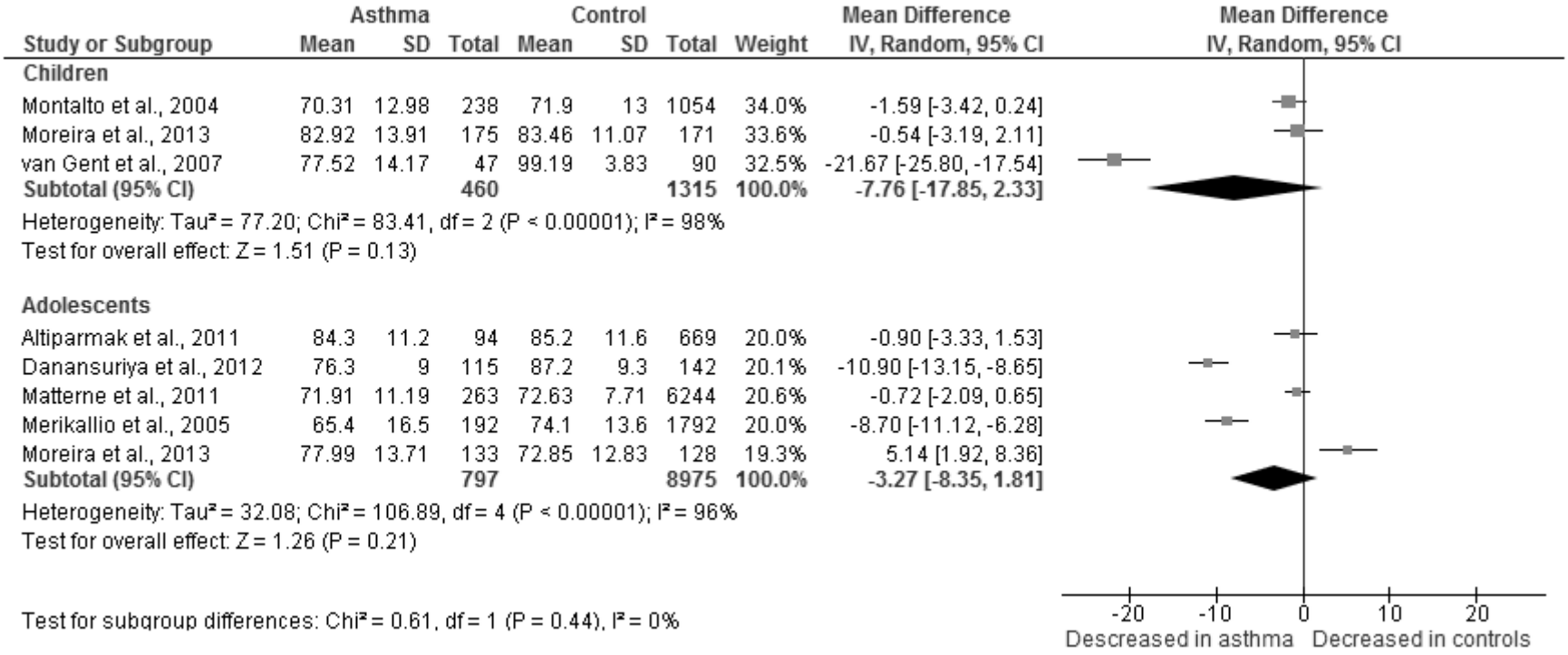

Figure S1.A | Forest plots for subgroup analyses by age group for children/adolescents' overall QoL

Supplementary Material

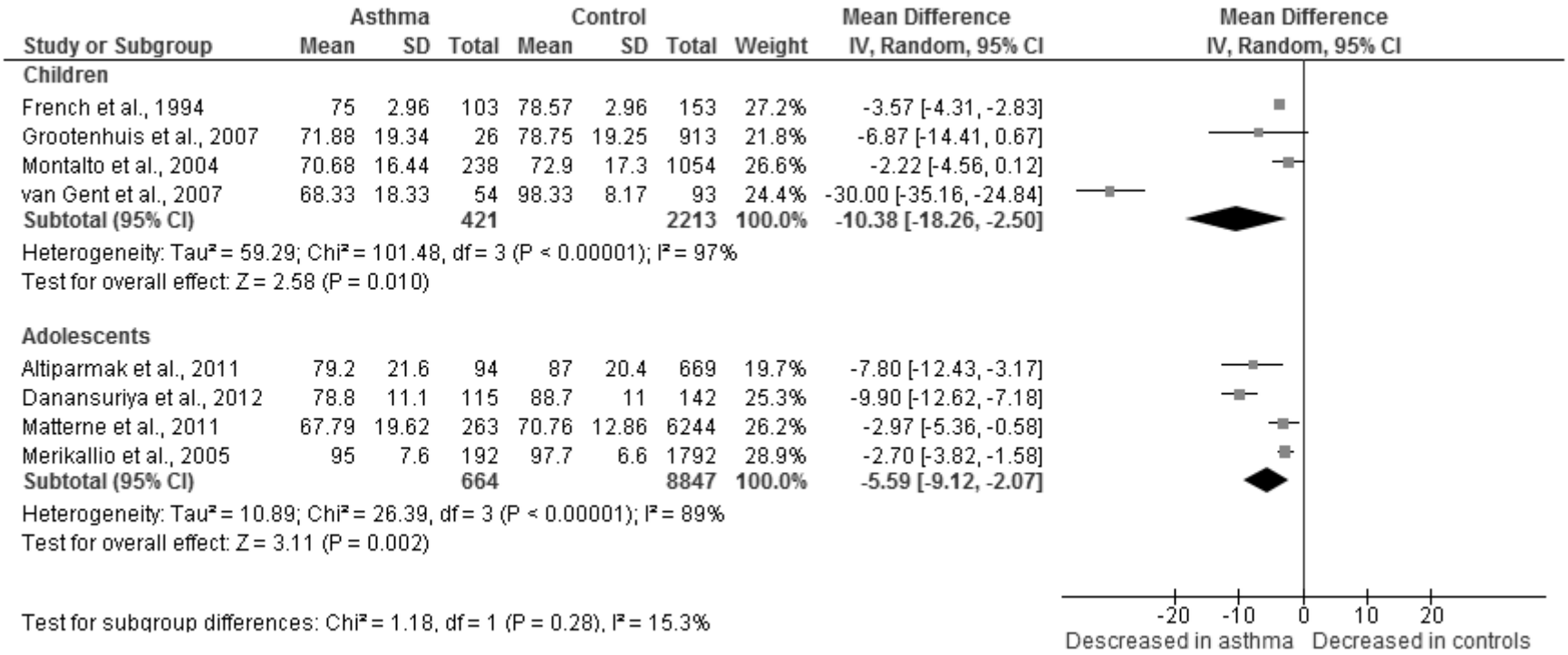

Figure S1.B | Forest plots for subgroup analyses by age group for children/adolescents' physical functioning

Supplementary Material

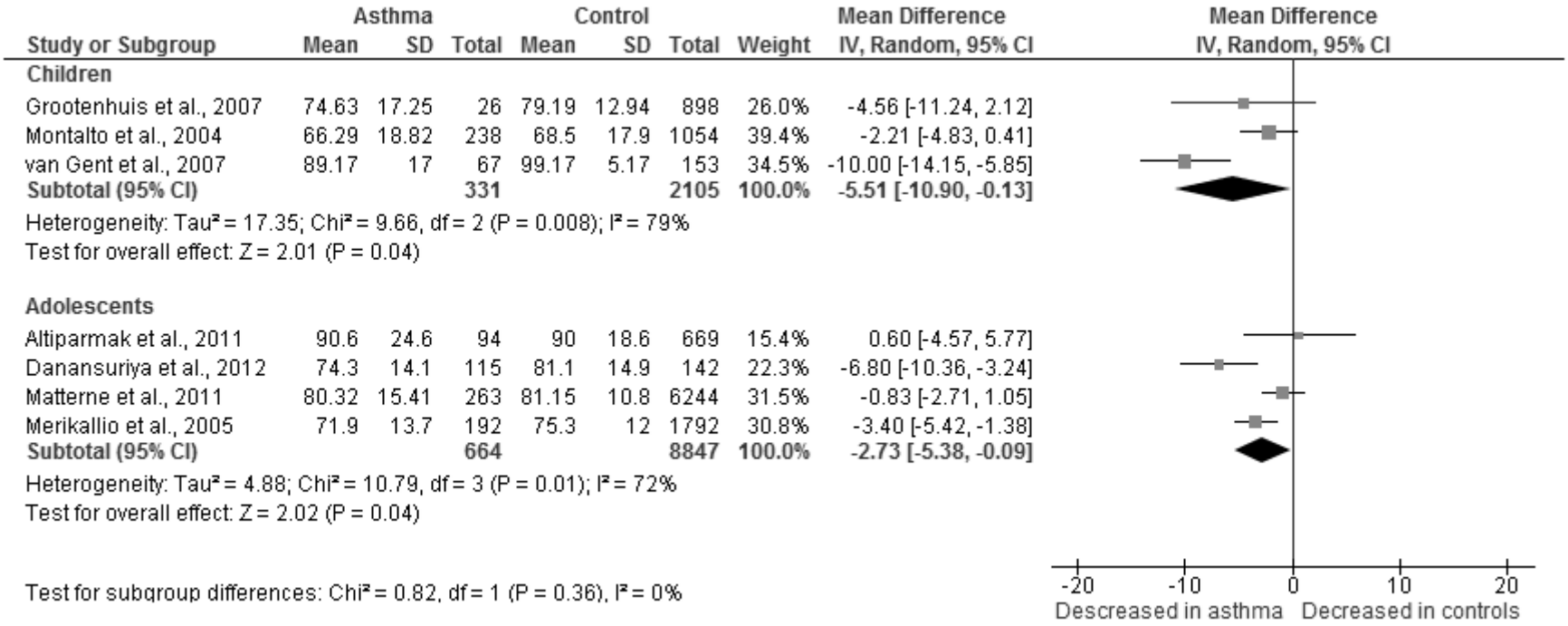

Figure S1.C | Forest plots for subgroup analyses by age group for children/adolescents' psychological functioning

Supplementary Material

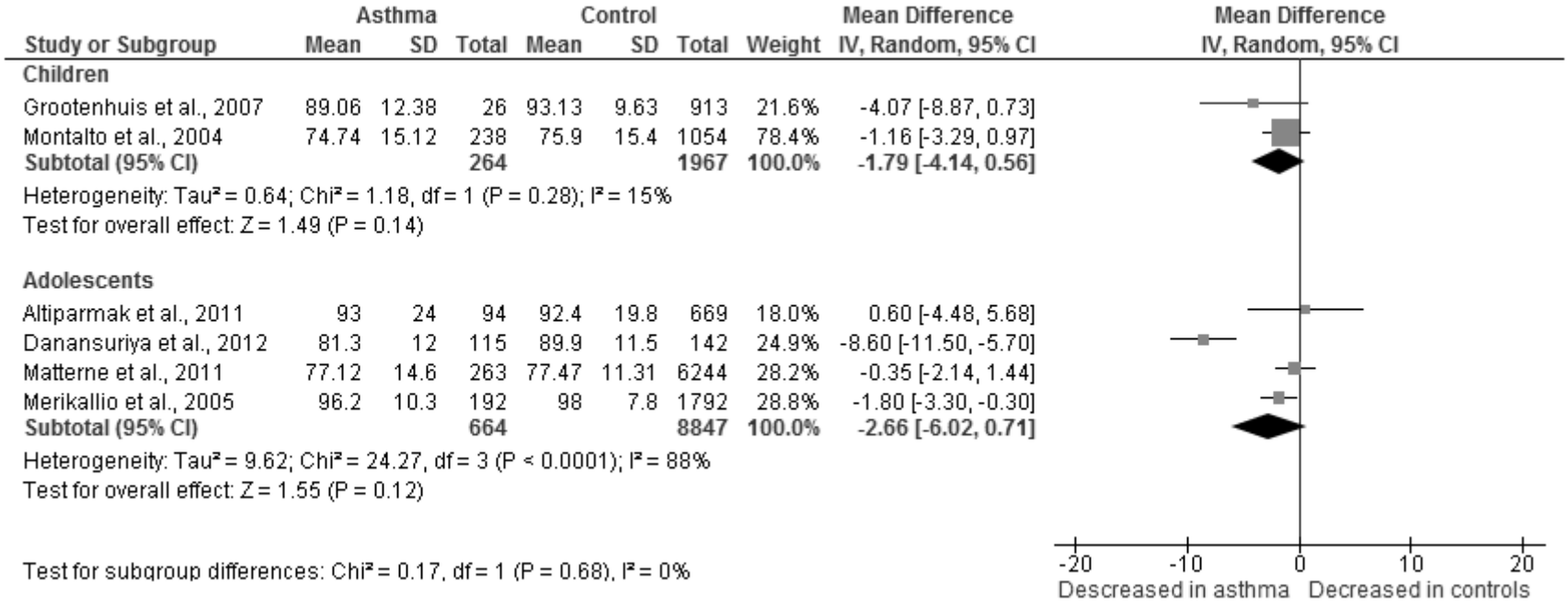

Figure S1.D | Forest plots for subgroup analyses by age group for children/adolescents' social functioning

Supplementary Material

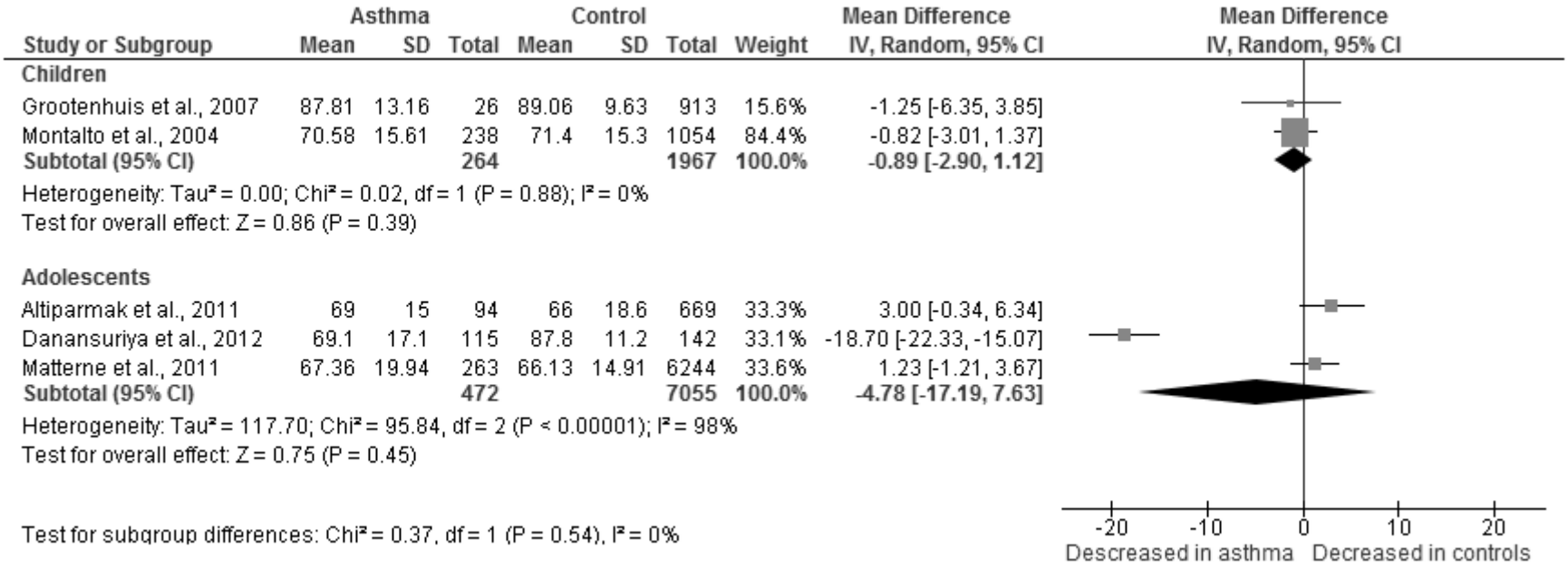

Figure S1.E | Forest plots for subgroup analyses by age group for children/adolescents' school functioning

Supplementary Material

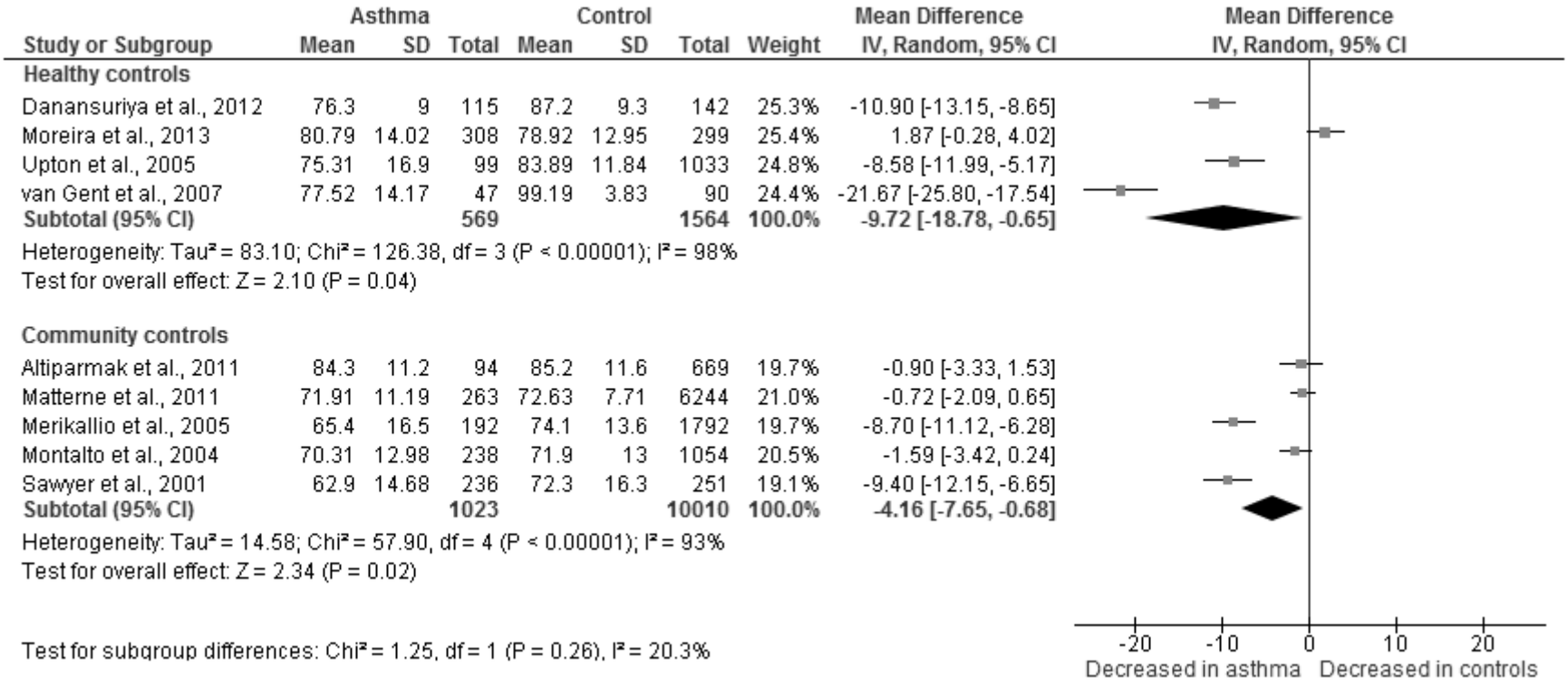

Figure S2.A | Forest plots for subgroup analyses by type of controls for children/adolescents' overall QoL

Supplementary Material

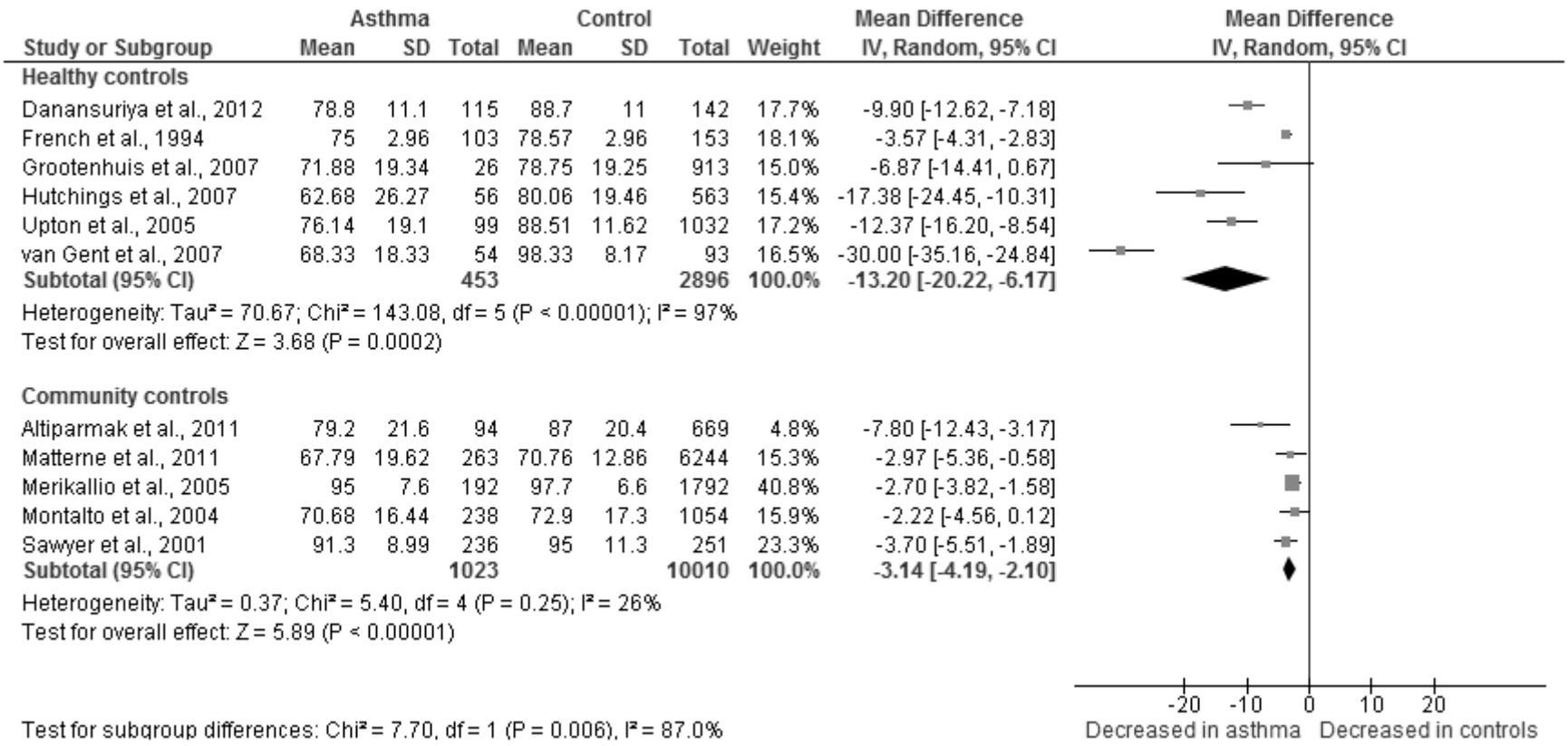

Figure S2.B | Forest plots for subgroup analyses by type of controls for children/adolescents' physical functioning

Supplementary Material

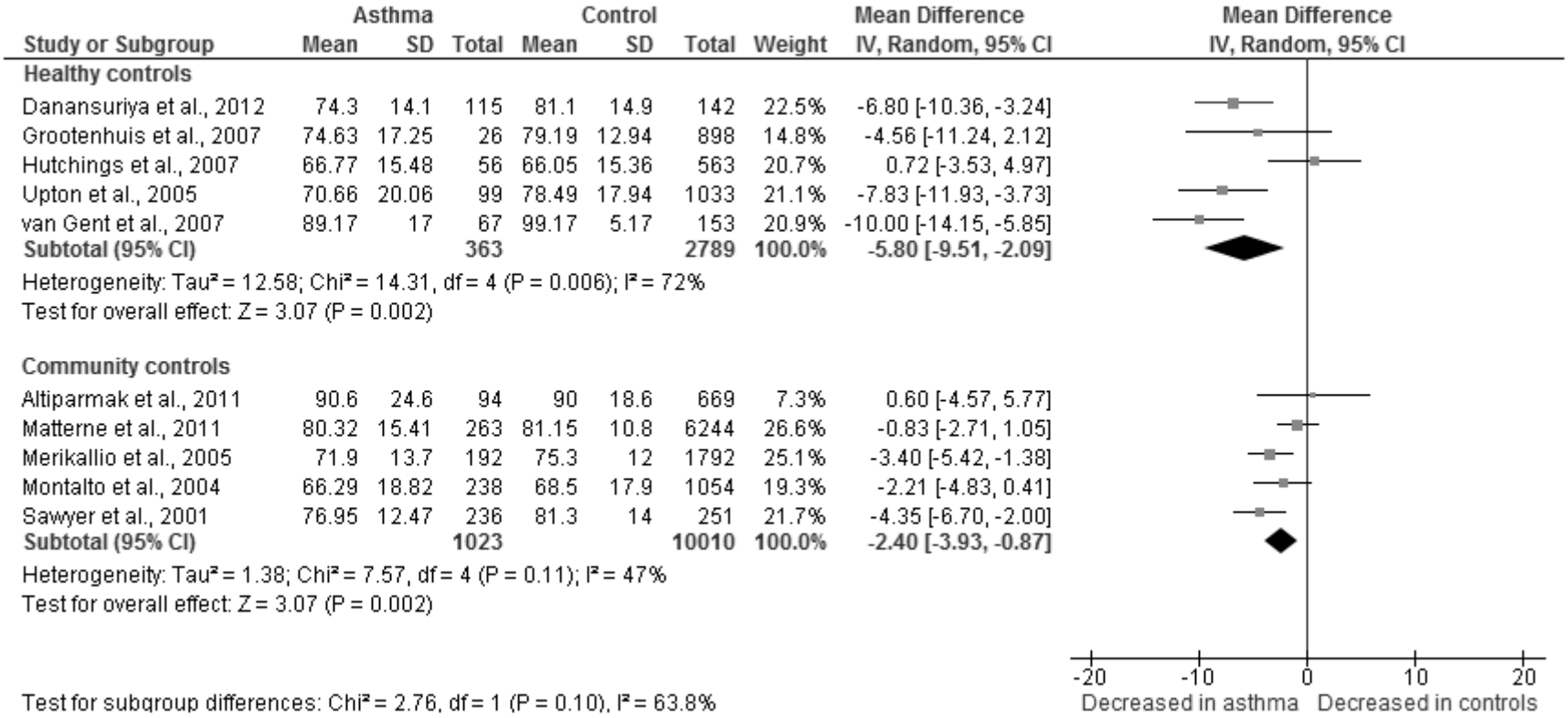

Figure S2.C | Forest plots for subgroup analyses by type of controls for children/adolescents' psychological functioning

Supplementary Material

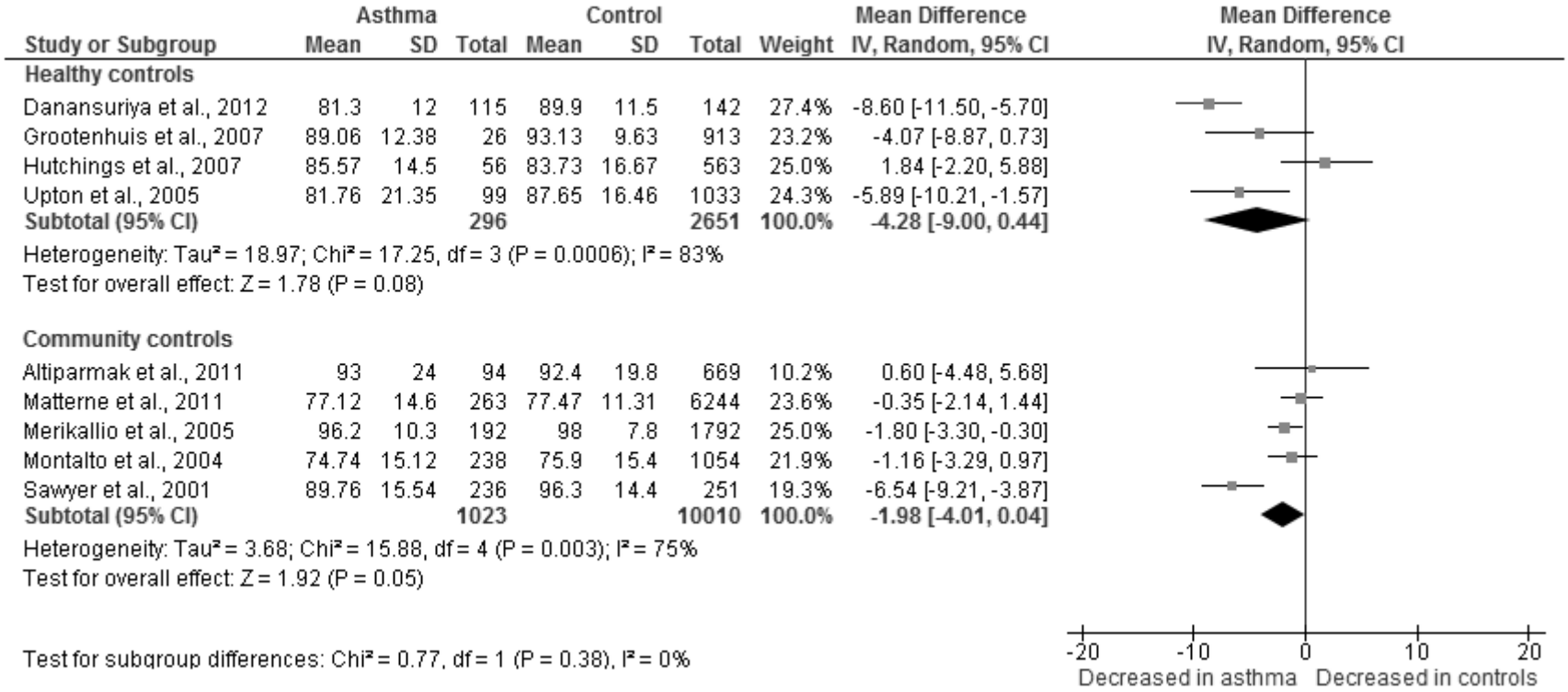

Figure S2.D | Forest plots for subgroup analyses by type of controls for children/adolescents' social functioning

Supplementary Material

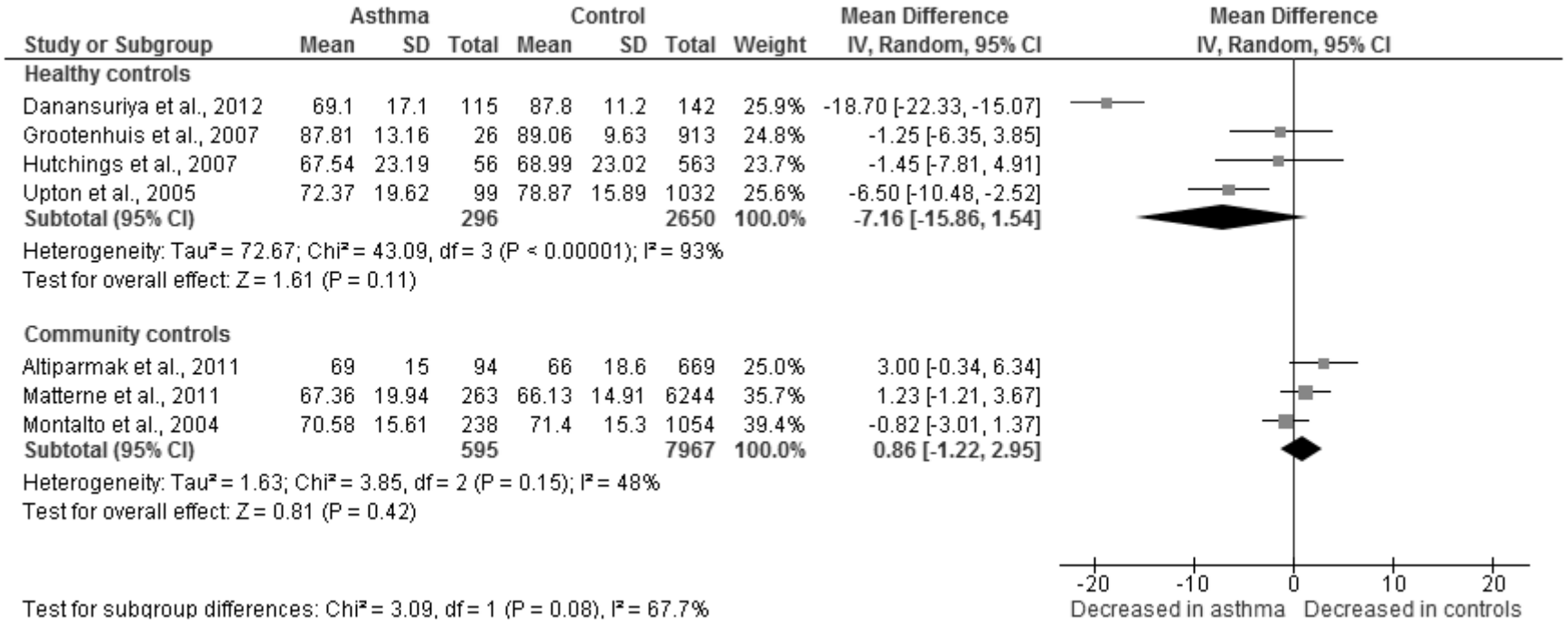

Figure S2.E | Forest plots for subgroup analyses by type of controls for children/adolescents' school functioning

Supplementary Material

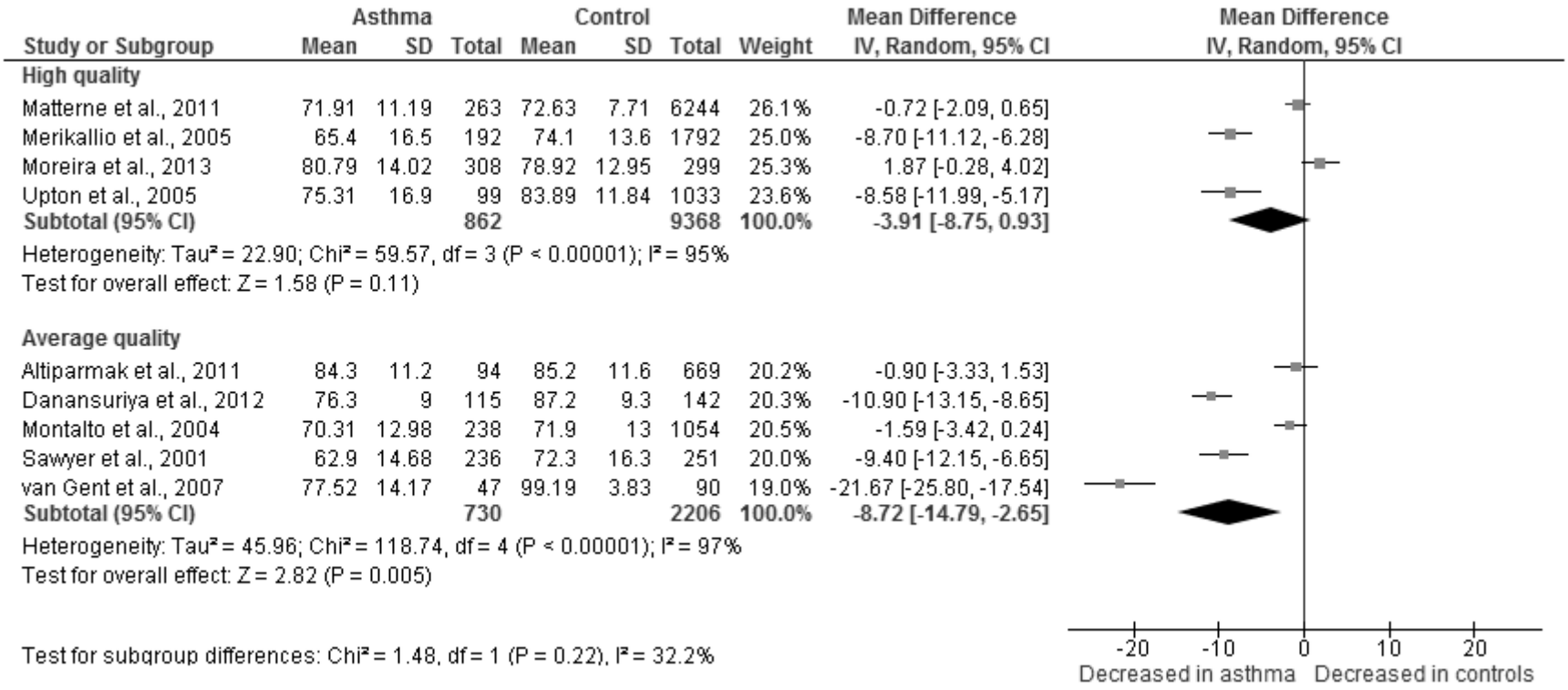

Figure S3.A | Forest plots for subgroup analyses by quality rating for children/adolescents' overall QoL

Supplementary Material

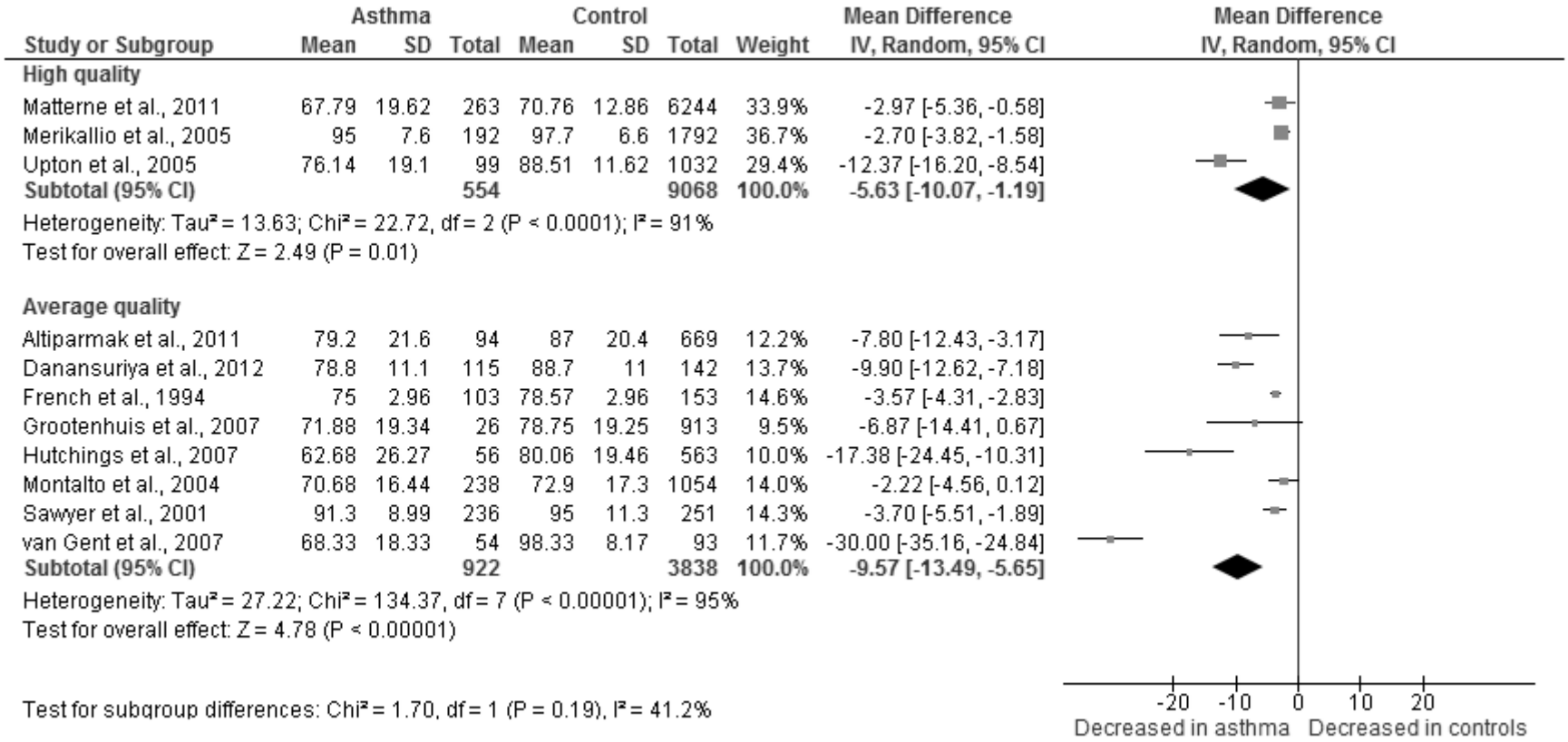

Figure S3.B | Forest plots for subgroup analyses by quality rating for children/adolescents' physical functioning

Supplementary Material

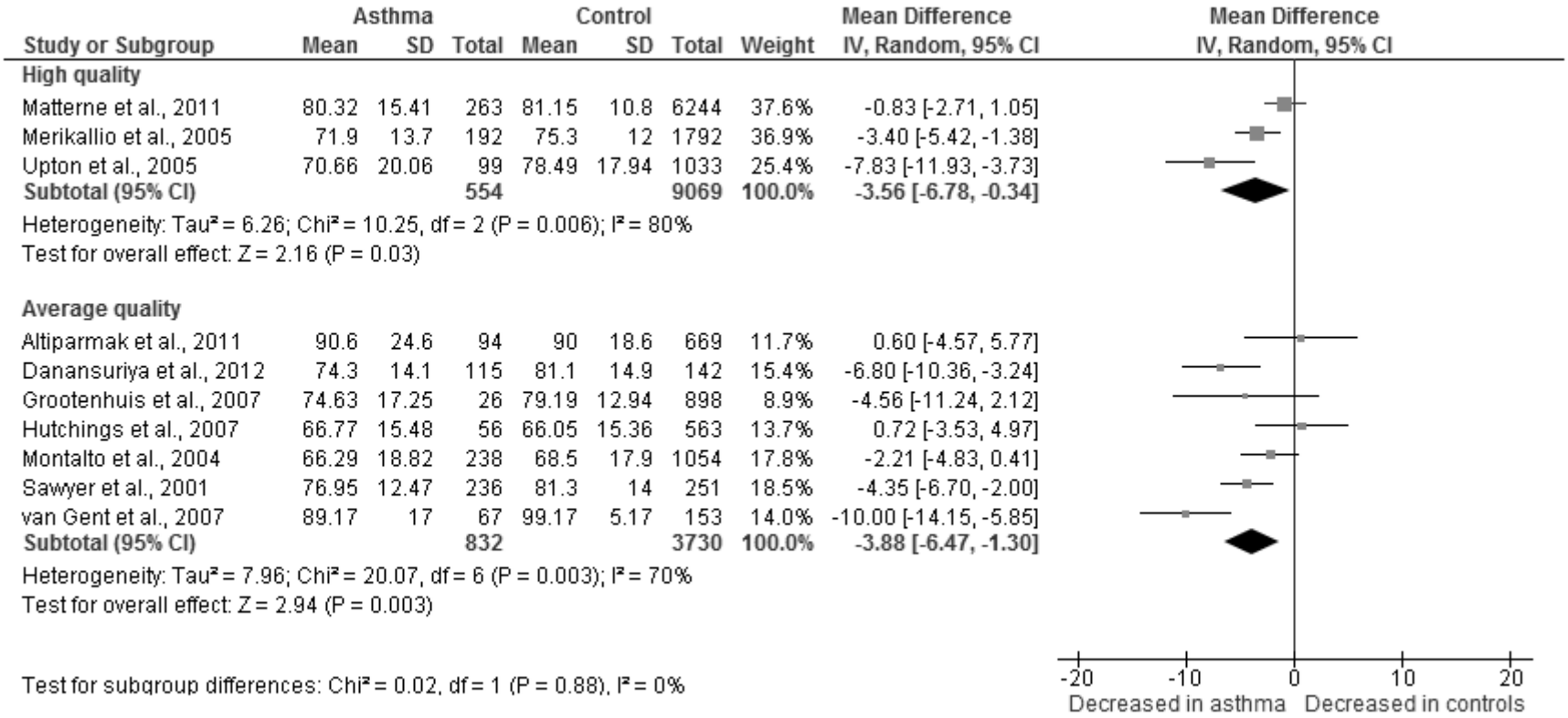

Figure S3.C | Forest plots for subgroup analyses by quality rating for children/adolescents' psychological functioning

Supplementary Material

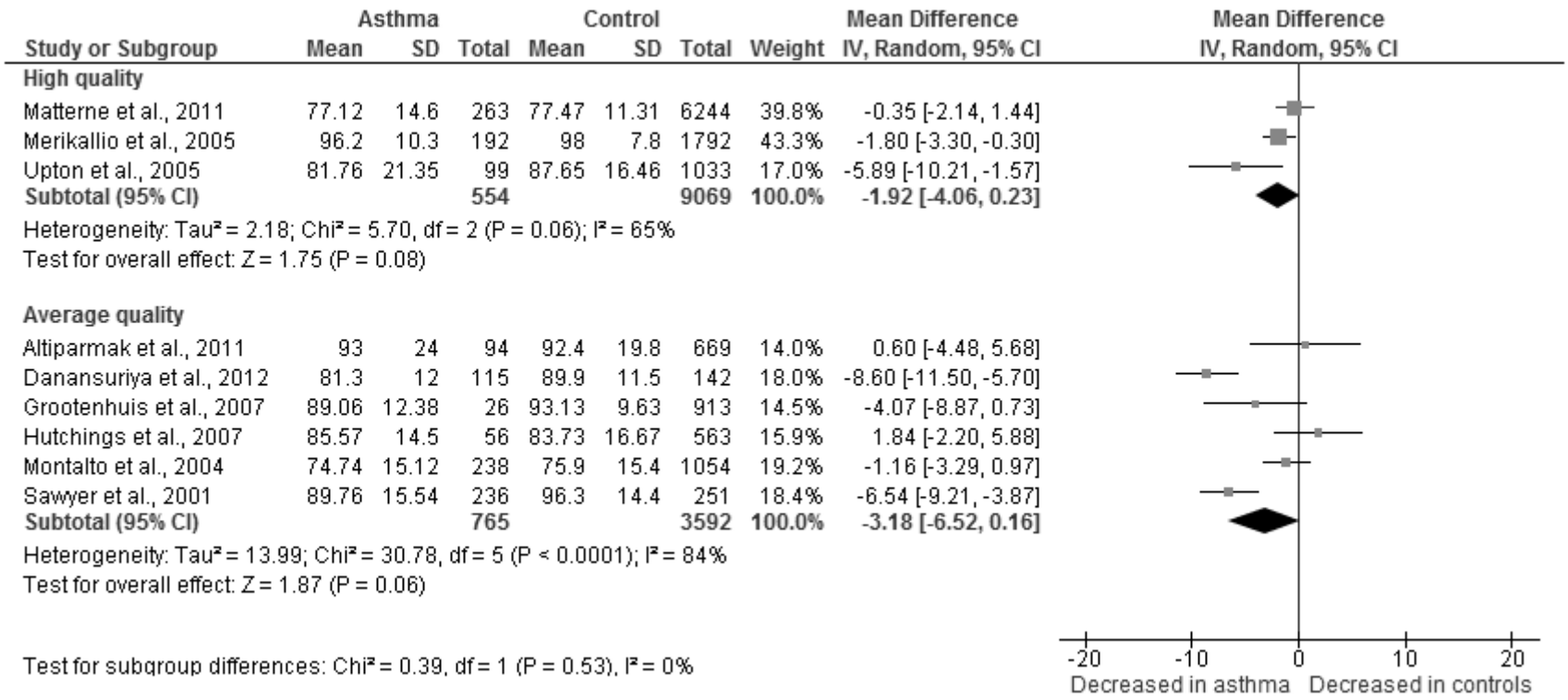

Figure S3.D | Forest plots for subgroup analyses by quality rating for children/adolescents' social functioning

Supplementary Material

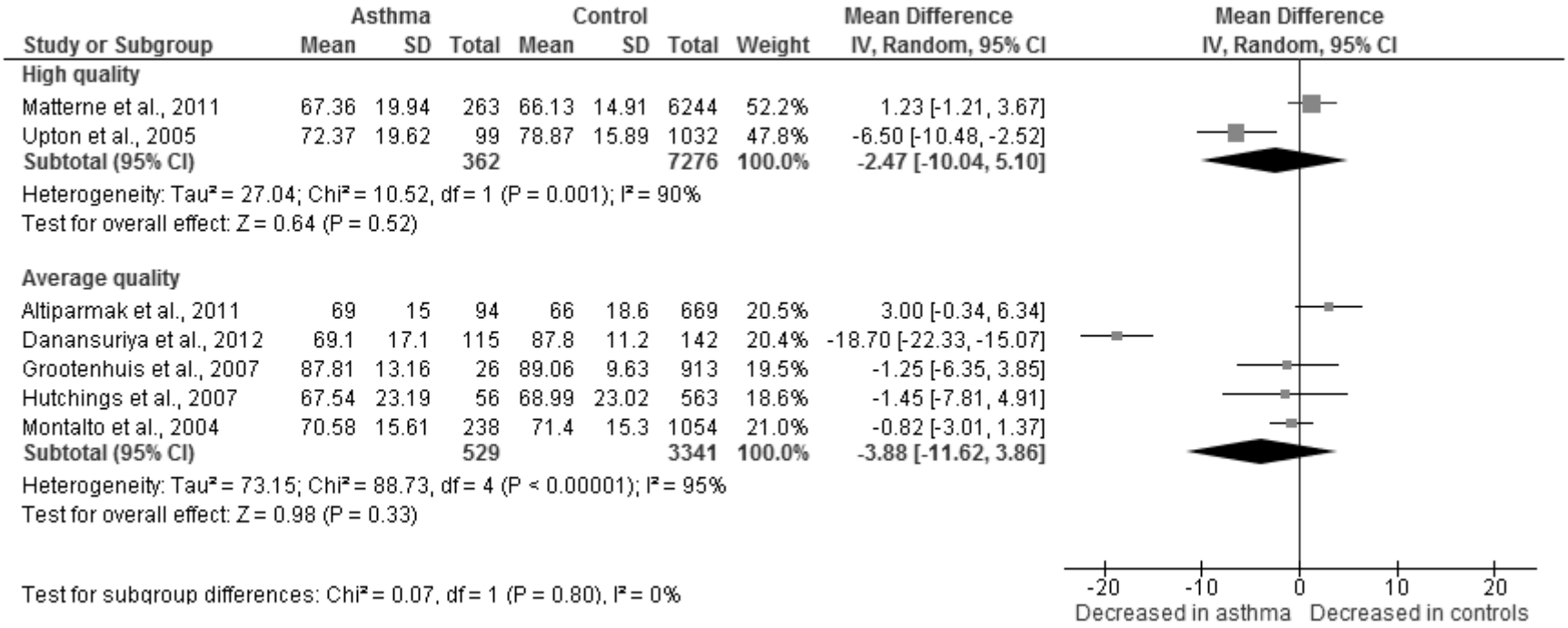

Figure S3.E | Forest plots for subgroup analyses by quality rating for children/adolescents' school functioning