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ORIGINAL ARTICLE

Depression and adherence to treatment in diabetic children and adolescents: a systematic review and meta-analysis of observational studies

Chuenjid Kongkaew · Katechan Jampachaisri · Chollapat A. Chaturongkul · C. Norman Scholfield

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Abstract Depression compromises diabetes treatment in juveniles, and this study aimed to identify influential targets most likely to improve adherence to treatment and glycemic control. Prospective observational studies investigating associations between depression and treatment adherence in juveniles with type 1 diabetes were extracted from MEDLINE, EMBASE, CINAHL, PsycINFO and Cochrane Central. Nineteen studies comprising 2,935 juveniles met our criteria. Median effect sizes between depression and treatment adherence were 0.22 (interquartile range (IQR), 0.16–0.35) by patient and 0.13 (IQR, 0.12–0.24) caregiver report. Corresponding values for depression/glycemic control were 0.16 (IQR, 0.09–0.23) and 0.08 (IQR, 0.04–0.14), respectively. Effect sizes varied with study design, publication year and assessment tools: CES-D yielded a higher effect size than other assessment tools for depression, where associations for depression and either adherence or glycemic control was investigated. Several behaviours influenced adherence and glycemic control. *Conclusion*: This study showed moderate associations between depression and poor treatment adherence. Targeting behaviour and social environments, however, may ultimately provide more cost-effective health gains than targeting depressive symptoms.

Keywords Diabetes type 1 · Non-adherence · Depression · Children · Adolescents

C. Kongkaew (✉) · C. N. Scholfield
Faculty of Pharmaceutical Sciences, Naresuan University, 99 Mu 9, NakhonSawan Road, Phitsanulok 65000, Thailand
e-mail: chuenjid@googlemail.com

K. Jampachaisri
Faculty of Sciences, Naresuan University, Phitsanulok, Thailand

C. A. Chaturongkul
Child Development & Neuropsychiatric Unit, Bangkok Medical Center, Bangkok, Thailand

Abbreviations

T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
EMBASE	Excerpta Medica Database
CINAHL	Cumulative Index to Nursing and Allied Health Literature
HbA1c	Haemoglobin A1c
CDI	Children's Depression Inventory
CES-D	Centre for Epidemiological Studies Scale for Depression
BASC	Behaviour Assessment System for Children
CDI-S	Children's Depression Inventory-Short Form
SCI	Self-Care Inventory
BGMF	Blood glucose monitoring frequency
DSMP	Diabetes Self-Management Profile
DMS	Diabetes Self-Management Scale
SCQ	Self-Care Questionnaire
IQR	Interquartile range
CI	Confidence interval

Background

Type 1 diabetes (T1DM) has been overshadowed by the type 2 diabetes (T2DM) pandemic but continues to represent a major global health challenge which includes 500,000 children less than 15 years [33] and is the third most prevalent chronic disease in this age group. Children and adolescents with T1DM have increased incidence of psychiatric disorders including anxiety, eating disorders and especially depression with a prevalence of ~20 % compared to ~10 % in non-diabetics [17, 32]. This is hardly surprising given the widespread action of insulin in the brain [23]. T1DM is primarily an irreversible autoimmune attack against pancreatic beta cells, and there are many compensatory hormonal and

inflammatory changes [42] which may exacerbate the depression [10, 45]. Such children are often found to have a negative self-perception, low self-esteem and an ineffective coping style [26] and may be exacerbated by maternal depression [32]. This linkage between depression and T1DM leads to continual disability and dependency with associated costly health care [58].

For children >5 years, the obvious treatment would be to prescribe antidepressants, but their effect on glycemic control have been mixed [56]; they depend on baseline values of haemoglobin A1c (HbA1c) [40], and high incidences of adverse effects have been reported [21]. Various psychological treatments for depressed children with T1DM appeared a little more consistent accompanied by some lowering of HbA1c [57]. Nevertheless, tight glycemic control using timely glucose monitoring, careful insulin dosing and strict attention to diet underpins normal development and academic attainment [49]. High adherence to the treatment can then foster a near normal development and lifespan but such a life-long treatment regime creates a heavy burden, and external influences threaten this adherence in T1DM children.

The World Health Organization defines adherence as 'the extent to which a person's behaviour-taking medication, following a diet and/or executing lifestyle changes — corresponds with agreed recommendations from a health care provider' [58]. Patients with depression and diabetes have reduced adherence to treatments, poor glycemic control and associated high HbA1c [27], higher hospital admissions and more diabetic complications [14]. Furthermore, depression is likely to be exacerbated by large glycemic excursions in already depressed children [27, 43, 48], while hypoinsulinemia is likely, in the long run, to place their neurocognitive development in jeopardy [24, 27].

Previous systematic reviews have focused on the prevalence of co-morbid depression in T1/2DM [1], depression and glycemic control in T1/2DM adults [39], depression and macrovascular diabetic complications in T1/2DM adults [8], depression and overall diabetes treatment in children and adults using self-reporting of depression [15]. A previous study tested the robustness of the association between depression and adherence and how some aspects of study methodologies affected this relationship [15], but the role of different tools, particularly those used to assess depression and adherence, has received less attention. Indeed, these factors have been shown to impact in studies on other morbid conditions accompanying depression (e.g. [12, 41, 55]). This information could also improve the way to assess adherence or depression.

Therefore, in the present systematic review and meta-analysis we address: (1) degree of association of non-adherence to treatment in children and/or adolescents with T1DM and the influences of study design, publication date, personnel reporting the adherence, assessment tools for depression and assessment tools for adherence on the reported effect size and (2) degree of associations between potential factors and adherence to diabetes treatment, glycemic control or depression.

Methods

Data source and study selection

The following inclusion criteria were used (1) original studies if they were prospective, observational and/or randomized control trials; (2) studies reporting the effect size of associations between depression and adherence to treatment or provided sufficient data to calculate such information; (3) studies that were conducted on children or adolescents with T1DM; and (4) any language.

Outcome measures

As all included studies used self/proxy questionnaires, they assessed some depressive symptoms as a surrogate for depression, a term we will continue to use. This review focuses on effect sizes for associations between depression and adherence to diabetes treatments as the primary outcome; the effect sizes of the associations of potential factors affecting treatment adherence or depression were secondary outcomes.

Search strategy

The following databases were searched since their inception dates to July 2012: MEDLINE, EMBASE, CINAHL, PsycINFO and Cochrane Central. The key terms 'diabetes mellitus', 'depression', 'children', 'adolescent', '(non) adherence,' and '(non) compliance' were used along with MeSH terms and EMTREE. Literature retrieval was supplemented by hand-searching the reference list of all identified articles.

Data extraction and manipulation

The data extracted comprised of associations between depression and treatment adherence and information about the study design (i.e. longitudinal, cross-sectional), and these were loaded into a data extraction form. Other information included study settings, study population, domains of treatment (i.e. overall treatment, HbA1c levels (as an indicator for glycemic control)) and tools for assessing adherence or depression.

Direct associations were used to determine the effect size of associations between depression and non-adherence to the diabetes treatment: thus one study (using the Sorbel test) [43] was not analysed. The Cochrane risk of bias and the component approach were adopted for assessing the study quality [19, 44].

Data analysis

The effect size (r) of the non-adherence to treatment was calculated if this value was not reported in the included studies but contained sufficient data for calculation. The effect size was calculated from the t test and χ^2 when r was not reported in the original studies [15, 37]. The effect size, in behavioural science research, can be considered small when $r \leq 0.1$, medium when $r = 0.25$ and large when $r \geq 0.40$ [6, 20]. A statistical test for heterogeneity was performed using the Cochran–Mantel–Haenszel method. Between-study heterogeneity was assessed using χ^2 and I^2 tests to determine the appropriateness to compute a meta-analytic summary estimate [20]. The summary weighted mean difference and 95 % confidence intervals (CI) were calculated based on a random-effects model using the Dersimonian–Laird method [11]. The results across these studies were summarized using the median and interquartile range (IQR) if there was a significant heterogeneity between studies. An effect size based on one study was not entered to heterogeneity test or meta-analysis. The stated purpose of a Cochrane review is to provide a synthesis of the available evidence on a given topic, but there is no clear current guidance of reporting systematic review with no or only one included study [59]. With only one study, the relevant effect size for the present review is reported as it appears in the included original paper, thus serves as a benchmark for that particular variable which otherwise could not be characterized.

The studies were subgrouped to explore possible reasons for heterogeneity by: the persons who assessed adherence (i.e., patient self-report, caregiver report), study design (i.e. cross-sectional, longitudinal), publication year (i.e., before 2000, 2000 to present), assessment tools for depression (i.e. Children's Depression Inventory (CDI), Centre for Epidemiological Studies Scale for Depression (CES-D), Behaviour Assessment System for Children (BASC)), and assessment tools for adherence (i.e. Self-Care Inventory (SCI), blood glucose monitoring frequency (BGMF), Diabetes Self-Management Profile (DSMP), questionnaire of Johnson et al. [28, 29] as adapted by [38, 51], Diabetes Self-Management Scale (DMS), Self-Care Questionnaire (SCQ) and interview). Test for publication bias (fail-safe number) expressed as the number of negative studies required to reduce the effect size below $r = 0.05$ were also calculated (STATA v10.0, StataCorp, College Station, USA).

Results

Study and patient characteristics

Nineteen observational studies met the inclusion criteria (Fig. 1) which comprised of an aggregate of 2,935 children and adolescents aged 8–18 years, and their general characteristics are described in Table 1.

Fourteen studies were based on patient self-reporting, to study associations between depression and overall treatment adherence [2, 16, 18, 22, 25, 31, 34, 38, 42, 46, 47, 51, 52, 54], and 14 studies reported associations between depression and glycemic control [3, 9, 16, 18, 22, 25, 26, 31, 34, 36, 42, 46, 51, 54]. In five studies based on the reports provided by caregivers, four studies reported the associations between

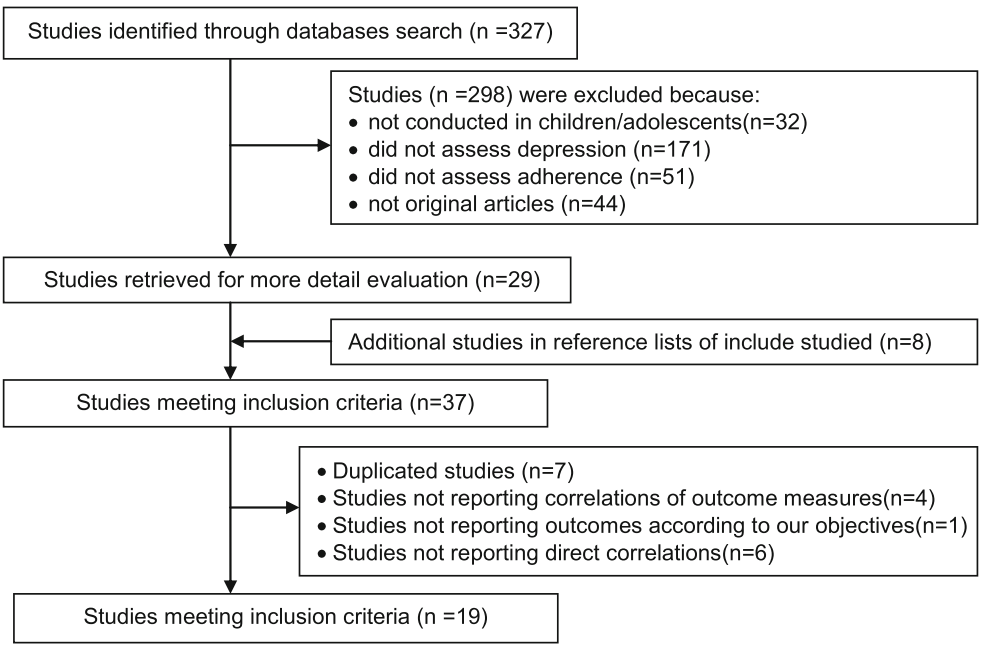

Fig. 1 The flow of the included studies

Table 1 Study characteristics of the included studies and effect sizes for adherence against depression both based on patient self-report

Authors (ref)	Country	Design of the study	No. participants (M/F)	Population (age range; mean)	Depression assessment tools	Adherence assessment tools	Effect size
Kuttner et al. [34]	USA	Prospective observational study (cross-sectional)	50 (20/30)	Children (10–16; 13.8±2.1)	CDI	Caregiver interview	**0.14** [a]
Grey et al. [16]	USA	Prospective observational study (cross-sectional)	103 pre- & adolescents (54/49)	Children (8–18; 12.9±3.0)	CDI	SCQ	**−0.07**
Littlefield et al. [38]	Canada	Prospective observational study (cross-sectional)	193 adolescents (90/103)	Children (13–18; 15.3)	CDI	Johnson questionnaire	**−0.50**
Lernmark et al. [36]	Sweden	Prospective observational study (cross-sectional)	62 children (25/37)	Children (9–18; 15.4±1.39)	CDI	NS	NS
Hood et al. [22]	USA	Prospective observational study (cross-sectional)	145 adolescents (64/81) 145 parents	Children (10–18; 14.9±2.3)	CDI	BGMF	**0.19** [a]
Naar-King et al. [46]	USA	Prospective observational study (cross-sectional)	119 children (61/58) 119 caregivers	Children (9.9–16.8;13.3±129)	BASC	DMS	**−0.23**
Storch et al. [52]	USA	Prospective observational study (cross-sectional)	167 children/ adolescents (60/107) 167 parents	Children (8–17; 12.8±2.5)	CDI-S	DSMP	**0.24** [a]
Butler et al. [2]	USA	Prospective observational study (cross-sectional)	78 children (41 /37) 78 mothers	Children (11.58–17.4;14.2)	CDI	SCI	**−0.32**
Korbel et al. [31]	USA	Prospective observational study (cross-sectional)	127 adolescents (65/62) 127 mothers	Children (10–15; 12.8)	CDI	SCI	**−0.44**
De Wit et al. [9]	Netherlands	Prospective observational study (cross-sectional)	91 adolescents (47/44) 91 parents	Children (13–17; 14.9±1.1)	CES-D	NS	NS
Nansel et al. [47]	USA	Prospective observational study (cross-sectional)	325 children 325 parents	Children (9–15.5; 12.5)	CDI	DSMP	**−0.38**
Jaser et al. [26]	USA	Prospective observational study (cross-sectional)	108 children 108 mothers	Children (8–12; 9.94±1.5)	CDI	NS	NS
Stewart et al. [51]	USA	Prospective observational study (longitudinal)	231 adolescent (92/139) 231 parents	Children (11–18; 13.9±1.8)	CES-D	Johnson question naire	**−0.35**
Helgeson et al. [18]	USA	Prospective observational study (longitudinal)	132 adolescents (62/70)	Children (10.73–14.21; 12.1)	CDI	SCI	**−0.20**
Butner et al. [3]	USA	Prospective observational study (longitudinal)	185 adolescents 185 parents	Children (10–14; 12.5±1.3)	CDI	SCI	NS
McGrady et al. [42]	USA	Prospective observational study (longitudinal)	144 adolescents (69/75) 144 caregivers	Children (13–18; 15.4±1.39)	CDI	BGMF	**−0.29**
Cunningham et al. [7]	USA	Prospective observational study (longitudinal)	147 adolescents (71/76) 147 caregivers	Adolescent (13–18; 15.5±1.40)	CES-D	NS	NS
Ingerski et al. [25]	USA	Prospective observational study (cross-sectional)	276 adolescents (154/122) 261 caregivers	Adolescent (13–18; 15.7±1.40)	CDI	BGMF	**0.16** [a]
Tran et al. [54]	USA	Prospective observational study (cross-sectional)	252 adolescents (117/135)	Adolescent (10–14; 12.5±1.53)	CDI	SCI	**0.21** [a]

The effect size was calculated from the *t* test and $\chi 2$ when *r* was not reported in the original studies. They usually were reported as crude values (no *p* value). The significance of the numbers will be summarized using meta-analytic approach in all study or subgroup analysis

CDI Children's Depression Inventory, *CES-D* Centre for Epidemiological Studies Scale for Depression, *BASC* Behaviour Assessment System for Children, *CDI-S* Children's Depression Inventory-Short Form, *SCI* Self-Care Inventory; *BGMF* blood glucose monitoring frequency, *DSMP* Diabetes Self-Management Profile, *DMS* Diabetes Self-Management Scale, *SCQ* Self-Care Questionnaire

[a] In these cases, only reported the effect sizes without indicating the direction

depression and overall treatment adherence [25, 46, 47, 51], and four studies reported associations between depression and glycemic control [7, 25, 46, 51].

Eight studies [16, 18, 26, 31, 34, 46, 47, 54] only included diabetic patients free of diagnosed psychosis, mental retardation, neurocognitive disorders or without other major chronic illness (e.g. cancer or rheumatoid arthritis); six studies [7, 25, 36, 42, 51, 52] specifically excluded patients with psychosis and five studies [2, 3, 9, 22, 38] did not report such criteria.

Heterogeneity and publication bias

Adherence to treatment Effect sizes based on the patient self-report for adherence to overall diabetes treatment and glycemic control were heterogeneous with high inconsistency. Effect sizes based on caregiver reports for adherence to overall diabetes treatment and glycemic control also showed high heterogeneity (corresponding χ^2, I^2 and fail-safe number in Table 2). Likewise, heterogeneity was apparent in each subgroup: by study design, publication year, assessment tools for depression and assessment for adherence (Table 3).

Other potential influences Heterogeneity testing on factors affecting adherence to overall diabetes treatment, glucose control and depression against socio-economic status and minority status yielded homogenous effect sizes, while gender, age and duration of diabetes were heterogeneous. Insulin delivery method was homogeneous against glucose control; however, it was heterogeneous against overall diabetes treatment and depression (Table 4).

Associations between depression and overall adherence to diabetes treatment

The 14 studies using patient self-reports [2, 16, 18, 22, 25, 31, 34, 38, 42, 46, 47, 51, 52, 54] and 4 studies using caregiver reports [25, 46, 47, 51] produced effect sizes falling in the medium range (Table 2).

Associations between depression and glycemic control

The median effect size was moderate for both the included studies using patient self-report (14 studies) [3, 9, 16, 18, 22, 25, 26, 31, 34, 36, 42, 46, 51, 54] and those using caregiver assessment (4 studies) [7, 25, 46, 51] (Table 2).

Study design, publication year and assessment tools of depression and for adherence

Longitudinal studies yielded higher effect sizes than cross-sectional studies with associations for depression against treatment adherence and against glycemic control. Depression was more strongly associated with adherence for studies conducted since 2000 compared to earlier years, but trend was reversed for depression versus glycemic control (HbA1c) during the same periods (Table 3).

The tools used to assess depression influenced the strength of the associations. Thus, CES-D yielded higher effect sizes than other tools for depression where associations for depression against adherence and against glucose control were investigated. The effect size for BASC was greater than CDI for studies assessing depression and adherence to overall treatment, while BASC yielded lower effect size than CDI for studies assessing depression and glycemic control.

Adherence as assessed by the Johnson questionnaire produced superior effect sizes than SCI > DSMP > DMS > BGMF > interview > SCQ (Table 3). In comparing depression with glycemic control, the highest to smallest effect sizes were SCI > SCQ=interview alone > BGMF > Johnson questionnaire > DMS (Table 3).

Potential factors influencing adherence to diabetes treatment

Table 4 lists 13 independent factors influencing adherence to overall treatment, glycemic control and depression. Twelve of these factors showed moderate effect sizes of 0.10–0.29 for adherence to overall treatment, while all 13 factors showed moderate effect sizes for glycemic control and for depression.

Table 2 Associations between depression and overall diabetes treatment adherence or glycemic control by patient self-report or caregiver report

Subgroups	No. studies	Effect size *r*	Heterogeneity test	Fail-safe *n*[a] (*r*=0.05)
Patient self-report				
Overall treatment adherence	14	**0.22** (IQR, 0.16–0.35)	(χ^2,189.2; *df*, 13; $p<0.0001$; I^2, 93.1 %)	**49**
Glycemic control	14	**0.16** (IQR, 0.09–0.23)	(χ^2, 78.0; *df*, 13; $p<0.0001$; I^2, 83.30 %)	**32**
Caregiver				
Overall treatment adherence	4	**0.13** (IQR, 0.12–0.24)	(χ^2, 50.7; *df*, 3; $p<0.0001$; I^2, 94.1 %)	**7**
Glycemic control	4	**0.08** (IQR, 0.04–0.14)	(χ^2, 21.0; *df*, 3 $p<0.0001$; I^2, 85.7 %)	**3**

IQR or SE are presented as variations of a measure of statistical dispersion for readers to justify the significance of the results

[a] Publication bias expressed as the number of negative studies required to reduce the effect size below $r=0.05$

Table 3 Subgroup analyses of effect size by study design; assessment tools for depression, publication year; assessment tools for adherence in the studies using patient self-report

Subgroups	No. studies (refs)	Effect size[a], *r* (variation)	Heterogeneity test
Adherence to overall treatment			
Study design			
Cross-sectional	**11** [2, 16, 22, 25, 31, 34, 38, 46, 47, 52, 54]	**0.21** (IQR, 0.14–0.27)	χ^2, 275; *df*, 10; $p<0.001$; I^2, 96.4 %
Longitudinal	**3** [18, 42, 51]	**0.29** (IQR, 0.20–0.35)	χ^2, 10.3; *df*, 2; $p=0.006$; I^2, 80.5 %
Publication year			
Before 2000	**3** [16, 34, 38]	**0.14** (IQR, 0.07–0.50)	χ^2, 97.7; *df*, 2; $p<0.001$; I^2, 98.0 %
Since 2000-present	**11** [2, 18, 22, 25, 31, 42, 46, 47, 51, 52, 54]	**0.23** (IQR, 0.19–0.35)	χ^2, 87.1; *df*, 10; $p<0.001$; I^2, 88.5 %
Assessment tools for depression			
CDI	**12** [2, 16, 18, 22, 25, 31, 34, 38, 42, 47, 52, 54]	**0.20** (IQR, 0.16–0.35)	χ^2, 175; *df*, 11; $p<0.001$; I^2, 93.7 %
CES-D	**1** [51]	**0.35** (SE, 0.031)	NA
BASC	**1** [46]	**0.23** (SE, 0.038)	NA
Assessment tools for adherence			
SCI	**3** [2, 31, 54]	**0.32** (IQR, 0.21–0.44)	χ^2, 21.2; *df*, 2; $p<0.001$; I^2, 90.6 %
BGMF	**3** [22, 25, 42]	**0.17** (CI, 0.14–0.20)	χ^2, 0.65; *df*, 2; $p=0.722$; I^2, 0.0 %
DSMP	**2** [47, 52]	**0.31** (IQR, 0.24–0.38)	χ^2, 10.8; *df*, 1; $p=0.001$; I^2, 90.7 %
Johnson Questionnaire	**2** [38, 51]	**0.42** (IQR, 0.35–0.50)	χ^2, 9.87; *df*, 1; $p=0.002$; I^2, 89.9 %
DMS	**1** [46]	**0.23** (SE, 0.04)	NA
SCQ	**1** [16]	**0.07** (SE, 0.02)	NA
Interview	**1** [34]	**0.14** (SE, 0.049)	NA
Glycemic control			
Study design			
Cross-sectional	**10** [9, 16, 22, 25, 26, 31, 34, 36, 46, 54]	**0.14** (IQR, 0.09–0.23)	χ^2, 46.5; *df*, 9; $p<0.001$; I^2, 80.6 %
Longitudinal	**4** [3, 18, 42, 51]	**0.20** (IQR, 0.10–0.25)	χ^2, 32.1; *df*, 3; $p<0.001$; I^2, 90.7 %
Publication year			
Before 2000	**3** [16, 34, 36]	**0.23** (IQR, 0.09–0.23)	χ^2, 7.91; *df*, 2; $p=0.02$; I^2, 74.7 %
Since 2000-present	**11** [3, 9, 18, 22, 25, 26, 31, 42, 46, 51, 54]	**0.14** (IQR, 0.09–0.23)	χ^2, 68.2; *df*, 10; $p<0.001$; I^2 85.3 %
Assessment tools for depression			
CDI	**11** [3, 16, 18, 22, 25, 26, 31, 34, 36, 42, 54]	**0.17** (IQR, 0.09–0.23)	χ^2, 55.8; *df*, 10; $p<0.001$; I^2, 82.1 %
CES-D	**2** [9, 51]	**0.24** (IQR, 0.14–0.35)	χ^2, 14.60; *df*, 1; $p<0.001$; I^2, 93.1 %
BASC	1 [46]	**0.08** (SE, 0.02)	NA
Assessment tools for adherence			
SCI	**3** [2, 31, 54]	**0.32** (2) (IQR, 0.21–0.44)	χ^2, 21.2; *df*, 2; $p<0.001$; I^2, 90.6 %
BGMF	**3** [22, 25, 42]	**0.15** (3) (CI, 0.12–0.18)	χ^2, 1.84; *df*, 2; $p=0.398$; I^2, 0 %
Johnson Questionnaire	**1** [51]	**0.14** (3) (SE, 0.02)	NA
DMS	**1** [46]	**0.08** (4) (SE, 0.02)	NA
SCQ	**1** [16]	**0.23** (1) (SE, 0.04)	NA
Interview	**1** [34]	**0.23** (1) (SE, 0.06)	NA

IQR or SE are presented as variations of a measure of statistical dispersion for readers to justify the significance of the results

CDI Children's Depression Inventory, *CES-D* Centre for Epidemiological Studies Scale for Depression, *BASC* Behaviour Assessment System for Children, *SCI* Self-Care Inventory, *BGMF* blood glucose monitoring frequency, *DSMP* Diabetes Self-Management Profile, *DMS* Diabetes Self-Management Scale, *SCQ* Self-care Questionnaire, *IQR* interquartile range, *CI* confidence interval, *SE* standard error, *df* degree of freedom

[a] This represents level of association, not direction of association

Discussion

This systematic review and meta-analysis suggests that depression is moderately associated with non-adherence to treatment in diabetic children and adolescents based on patient self-report. The findings are consistent with those of a previous meta-analysis based on ten studies where the effect size was 0.29 [15] compared to the effect size of 0.22 in this study. This demonstrates that depression may be one of the underlying and persisting risks which compromise the treatment of

Table 4 Potential factors affecting adherence to diabetes treatment, glucose control and depression

Independent factors	Dependent factors	n studies (refs)	Effect size[a]	Heterogeneity test
Gender	Adherence	**7** [2, 18, 25, 31, 34, 46, 54]	**0.06** (IQR, 0.05–0.07)	χ^2, 27.4; *df*, 6; $p<0.001$; I^2, 78.1 %
	Glycemic control	**8** [2, 7, 18, 25, 31, 34, 46, 54]	**0.09** (IQR, 0.05–0.13)	χ^2, 33.8; *df*, 7; $p<0.001$; I^2, 79.3 %
	Depression	**9** [2, 3, 18, 22, 25, 31, 34, 46, 54]	**0.13** (IQR, 0.07–0.16)	χ^2, 41.2; *df*, 8; $p<0.001$; I^2, 80.6 %
Age	Adherence	**7** [2, 16, 18, 25, 31, 34, 54]	**0.08** (IQR, 0.06–0.25)	χ^2, 70.1; *df*, 6; $p<0.001$; I^2, 91.4 %
	Glycemic control	**9** [3, 7, 16, 18, 25, 31, 34, 36, 54]	**0.15** (IQR, 0.08–0.17)	χ^2, 89.1; *df*, 8; $p<0.001$; I^2, 91.0 %
	Depression	**9** [2, 3, 16, 18, 25, 31, 34, 36, 54]	**0.08** (IQR, 0.02–0.15)	χ^2, 97.5; *df*, 7; $p<0.001$; I^2, 92.8 %
Duration of diabetes	Adherence	**5** [18, 25, 31, 34, 54]	**0.12** (IQR, 0.1–0.21)	χ^2, 22.0; *df*, 4; $p<0.001$; I^2, 81.8 %
	Glycemic control	**6** [7, 18, 25, 31, 34, 54]	**0.12** (IQR, 0.09–0.14)	χ^2, 45.7; *df*, 5; $p<0.001$; I^2, 89.1 %
	Depression	**5** [18, 25, 31, 34, 54]	**0.05** (IQR, 0.03–0.14)	χ^2, 23.3; *df*, 4; $p<0.001$; I^2, 82.8 %
Socio-economic status	Adherence	**2** [18, 34]	**0.07** (95 % CI, 0.04–0.11)	χ^2, 2.82; *df*, 1; $p=0.093$; I^2, 64.5 %
	Glycemic control	**2** [18, 34]	**0.21** (95 % CI, 0.15–0.26)	χ^2 0.98; *df* 1; $p=0.323$; I^2 0.00 %
	Depression	**2** [18, 34]	**0.13** (95 % CI, 0.08–0.18)	χ^2 0.46; *df* 1; $p=0.498$; I^2 0.00 %
Minority status	Adherence	**1** [25]	**0.12** (NA)	NA
	Glycemic control	**2** [7, 25]	**0.20** (95 % CI, 0.16–0.24)	χ^2, 0.52; *df*, 1; $p=0.470$; I^2, 0.00 %
	Depression	**2** [7, 25]	**0.06** (IQR, <0.01–0.12)	χ^2, 19.61; *df*, 1; $p<0.001$; I^2, 94.9 %
Insulin delivery method	Adherence	**3** [18, 25, 54]	**0.09** (IQR, 0.04–0.28)	χ^2, 57.03; *df*, 2; $p<0.001$; I^2, 96.5 %
	Glycemic control	**4** [7, 18, 25, 54]	**0.30** (95 % CI, 0.27–0.33)	χ^2, 2.57; *df*, 3 $p=0.463$; I^2, 0.00 %
	Depression	**4** [7, 18, 25, 54]	**0.08** (IQR, 0.04–0.12)	χ^2, 43.30; *df*, 3; $p<0.001$; I^2, 93.10 %
Body mass index	Adherence	**1** [18]	**0.26**	NA
	Glycemic control	**1** [18]	**0.23**	NA
	Depression	**1** [18]	**0.35**	NA
Tanner stage	Adherence	**1** [34]	**0.07**	NA
	Glycemic control	**1** [34]	**0.27**	NA
	Depression	**1** [34]	**0.14**	NA
General psychopathology	Adherence	**1** [51]	**0.45**	NA
	Glycemic control	**1** [51]	**0.19**	NA
	Depression	**1** [51]	NA	NA
Puberty status	Adherence	**1** [18]	**0.15**	NA
	Glycemic control	**1** [18]	**0.18**	NA
	Depression	**1** [18]	**0.15**	NA
Parental relationship	Adherence	**1** [18]	**0.29**	NA
	Glycemic control	**1** [18]	**0.01**	NA
	Depression	**1** [18]	**0.16**	NA
Parental diabetes support	Adherence	**1** [18]	**0.24**	NA
	Glycemic control	**1** [18]	**0.06**	NA
	Depression	**1** [18]	**0.04**	NA
Support by friends	Adherence	**1** [18]	**0.11**	NA
	Glycemic control	**1** [18]	**0.16**	NA
	Depression	**1** [18]	**0.10**	NA

IQR or SE are presented as variations of a measure of statistical dispersion for readers to justify the significance of the results

IQR interquartile range, *CI* confidence interval, *df* degree of freedom, *NA* not applicable

[a] This represents level of association, not direction of association

juvenile T1DM patients. These findings have practical implications for juvenile diabetic patients where routine psychological assessment will identify those at risk of depression and facilitate prevention of depression, hence improving treatment [4].

Variations for effect sizes between depression and adherence to treatment were observed, which depend on study methodologies, particularly the person reporting adherence (patient or caregiver) and assessment tools for adherence or

depression. Such an association based on caregiver reporting seems to be smaller than that based on patient self-reporting. The reason for this discrepancy is not obvious as in other diseases [5, 13, 50] but may reflect caregivers lacking insight in the depressive symptoms of the child or patients overestimating adherence. The present findings also suggest that assessment tools affect the level of association but no one tool stands out as being superior. Given that many assessment tools have been deployed, the choice of assessment tool is more dependent on other considerations: clinical experience and sensitivity of tools for specific target group of patients. Careful selection of assessment tools is essential for measuring both adherence and depression which clearly need addressing in future studies. Nevertheless, an objective clinical endpoint (e.g. HbA1c) is a reliable metric because it integrates the major antidiabetic treatments including insulin, diet, exercise and stress management. In the later studies (Table 3), depression had an increased influence to overall adherence. However, depression had less influence on glycemic control, perhaps reflecting the improved technology (long-acting insulins and less painful glucose monitoring). Furthermore, effective interventions tackling other aspects of adherence to diabetes treatment (e.g. life style changes) may have also improved diabetes treatment in these juveniles with T1DM and depression.

This review provides pointers to potential factors affecting adherence to treatment, glycemic control and depression. Health-care professionals should be aware of these factors, especially modifiable ones with strong associations (e.g. physical factors such as BMI and method of insulin delivery and social influences such as interactions among parents of patients, teachers and peers). Parental advice and psycho-socio-economic support, as well as providing the children with adequate psychosocial needs, either via adjunctive use of individual or group psychotherapy, focusing on self-value and esteem, along with the use of proper antidepressants could effectively help the children in overcoming these impediments to adherence. Such treatments, when combined, are likely to be mutually reinforcing [30] and in the long-term be far more cost-effective than singling out a single behaviour to target. Investigations of other biological and behavioural factors exacerbating depression (e.g. sedentary life, poor self-care and stress-induced hypercortisolemia) are needed in further studies. More fundamentally, all previous work was conducted in the high income countries of North America and northern Europe (Table 1), and technical advances alone should further improve adherence. In low socio-economic countries, an assessment of depression and adherence is urgently needed since this will be relevant to treatment for many years to come.

The findings have some weaknesses. The associations were derived by univariate analyses to eliminate other interfering factors but not fully reflecting the complexity of adherence in real world. Due to noise/heterogeneity (e.g. inconsistent measurement) attached to measured variables in behavioural studies, more powerful and focused clinical studies are needed before associations between these potential factors and adherence to treatment are more clearly understood [6]. We attempted to assess the quality of the studies using 'Cochrane risk of bias', but the methodological information in the included studies was not explicitly reported [35].

Our review confirmed the associations between depression and adherence to medication, or glycemic control, determined by several metrics and extended how the association varied by study design and assessment tools for depression and for adherence. Well-accepted bibliographic databases were used to identify the included studies, and our review adheres to the standard guideline for meta-analysis of observational studies in epidemiology [53]. Efforts in minimizing the chance of having missed English studies that meet the inclusion criteria were made through additional hand-searches of the publication reference lists.

Conclusion

This study showed an association between depression and poor treatment adherence, and the results suggest that adherence might be improved by targeting behaviour and the social environment.

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