Executive Function Mediates the Link between Externalizing Behavior and HbA1c
in Children and Adolescents with Type 1 Diabetes:

A Cross-national Investigation

Running title: Executive Function and Externalizing Behavior

Eveline R. Goethals, PhD^{1,2}

Jurgen Lemiére, PhD¹

Frank J. Snoek, PhD³

Kristina Casteels, MD, PhD^{1,4}

Koen Luyckx, PhD^{1,5}

Maartje de Wit, PhD³

¹KU Leuven, Leuven, Belgium, ²Joslin Diabetes Center, Harvard Medical School, Boston, US,

³Amsterdam UMC, Amsterdam, Netherlands, ⁴University Hospital Leuven, Leuven, Belgium,

⁵UNIBS, University of the Free State, Bloemfontein, South Africa

Correspondence should be sent to Eveline R. Goethals, KU Leuven, Faculty of Psychology and Educational Sciences, Tiensestraat 102 box 3717, 3000 Leuven, Belgium. Tel: +32 16 32 82 46 - fax: +32 16 325916 - E-mail: Eveline.Goethals@kuleuven.be

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Accepted Article

OBJECTIVE Externalizing behavior (i.e., conduct problems, hyperactivity) and executive function (EF) problems in children and adolescents with type 1 diabetes (T1D) have been associated with worse diabetes-related and psychosocial outcomes but have not been examined in relationship to each other. We aimed to examine whether externalizing behavior is associated with HbA1c and whether this relationship is mediated by EF problems, specifically metacognition (i.e., ability to initiate, plan, organize and monitor behavior) and behavioral regulation (i.e., impulse control, regulation of emotion and behavior).

RESEARCH DESIGN AND METHODS Cohorts of Belgian and Dutch parents of children and adolescents (6-18 years) with T1D filled out questionnaires on externalizing behavior (Strengths and Difficulties Questionnaire; SDQ) and EF (Behavior Rating Inventory of Executive Function ;BRIEF) composite scales. Treating physicians collected HbA1c values. Mediation analyses were performed separately for the BRIEF composite Metacognition and Behavior Regulation scales, correcting for age, sex and diabetes duration.

RESULTS 335 parents of children and adolescents with T1D (mean age 12.3 $\pm$ 2.8 SD; mean HbA1c 7.6% $\pm$ 1.1 SD (60 mmol/mol $\pm$ 12.0 SD); mean diabetes duration 5.3 $\pm$ 3.6 SD; 49.6% female) participated. Analyses showed that the association between externalizing behavior and HbA1c is mediated by metacognition (ab path Point estimate=.05 BCa CI 95% .02-.08), and not behavioral regulation.

CONCLUSIONS Results uncovered the influence externalizing behavior may have on EF problems in the metacognition domain, which in turn seem to influence HbA1c. Clinicians should be mindful of these EF problems when working with children and adolescents displaying externalizing behavior, and not only target behavioral but also cognitive processes.

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INTRODUCTION

Despite improved diabetes technologies (1; 2), glycemic control remains suboptimal in youth with type 1 diabetes (T1D) and only a minority reach the HbA1c target levels (3; 4). As current guidelines set the HbA1c target (5; 6), even less children and adolescents may be able to achieve optimal glycemic control in the future.

Childhood and adolescence are challenging developmental stages. An abundance of research demonstrates that youth are at risk for psychosocial and psychiatric problems, which are associated with worse self-management and glycemic control (7; 8). However, to date, diabetes research tends to focus mainly on internalizing behavior difficulties such as depression, anxiety, distress (9), and risk behaviors such as disturbed eating (10). Despite their link to worse glycemic control in children and adolescents with T1D (11-13), externalizing behavior problems remain relatively understudied, and thus potentially under-assessed in clinical practice. Externalizing problems consist of inapp (overactivity, aggression). Evidence from a large population-based cohort study (8) points to increased risk in children and adolescents with T1D of, for example, attention deficit hyperactivity disorder (ADHD) and behavioral disorders compared to healthy matched controls. Further, there is ample general research linking externalizing behavior to worse outcomes in terms of mental and general health, health-related quality of life, educational level and social adaptation (14-17).

Moreover, certain subdomains of executive function (EF) -a variable that is rapidly gaining interest in diabetes research (18-21)- have been put forward as a link between externalizing behavior and outcomes. EF is an umbrella term referring to a set of diverse, higher-order cognitive skills including inhibition, cognitive flexibility, sustaining attention, planning and organizing (22; 23). These competencies are distinctively important for performing the multiple

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daily diabetes self-management tasks (e.g., switching to diabetes care when a child is engaged in a different activity, anticipating when and how to deliver insulin,...). Thus far, EF is commonly measured by means of the Behavior Rating Inventory of Executive Function (BRIEF); (24; 25), an ecologically valid measure of EF capabilities within normal life. The BRIEF taps into two subdomains of EF: (1) behavioral regulation, encompassing the ability to cognitively shift from one situation to another, inhibit impulses, and regulate behavioral and emotional responses, and (2) metacognition, tapping into the ability to plan and organize, monitor behavior and working memory.

In the general population, EF has been identified as playing a role in the development and continuance of externalizing behavior (26-28). EF supports goal-directed behavior and is believed to play a crucial role in the self-regulation of behavior and emotions (22; 23). Youth with strong EFs may be more competent in planning and organizing, and regulating emotions, and thus suppressing potential externalizing behavior and/or regulating the negative emotions associated with externalizing behavior (e.g., anger). EF problems have been suggested as a mediating link between externalizing problem behavior problems and outcomes such as academic achievement in children and adolescents (29). Putting it positively, strong EFs have been forwarded as a protective factor in the relation between risk factors (26). Likewise, with diabetes self-management requiring higher EF-related cognitive skills, we could expect that in children and adolescents with T1D as well, the association between externalizing behavior and HbA1c is mediated by EF. However, to date, most diabetes research investigated a direct link between EF and diabetes outcomes (e.g., (18; 20), and only a few studies focused on the distinct competencies related to behavioral regulation and metacognition, respectively (21; 30; 31). So, based upon previous research and inspired by clinical practice, in which behavior problems regularly arise, we examined whether the link between externalizing behavior and glycemic control is mediated

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by EF, specifically metacognition and behavioral regulation. We hypothesized that both behavioral regulation and metacognition would function as mediators between externalizing behavior and glycemic control. Here we joined research forces and applied a cross-national perspective, joining baseline data of two databases from Belgium and the Netherlands, which resulted in a relatively large research sample of parents reporting on children and adolescents with T1D (6-18 years).

RESEARCH DESIGN AND METHODS

Participants and procedure

For this parent-reported study, we joined baseline data of two studies in children and adolescents with T1D from Belgium and the Netherlands (20; 32). The Belgian data were retrieved from a cross-sectional multi-center questionnaire study. Parents of eligible youth were invited by an email sent by their respective diabetes teams. The email included a description of the study, and a secured link to the questionnaires. After completing the informed consent, the questionnaires could be filled out. There was no monetary compensation. The data from the Netherlands were baseline data from a longitudinal multi-center cohort study with four yearly measurements. Eligible children and their parents were invited by their diabetes team by mail. After completing informed consent, questionnaires were completed online or on paper at home when requested. Children received a voucher of 10 euros when they completed the questionnaires. Both the Belgian and Dutch data-collection included adolescents and parents. For the current study aim, we only used parent-reports.

For the current study, parents of children and adolescents with T1D meeting the following (Belgium) and aged 8-15 years (the Netherlands), and (3) Dutch speaking. They were recruited from 7 Belgian and 5 Dutch hospitals. Exclusion criteria were cognitive disabilities. In the

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Belgian sample, parents of children and adolescents with psychiatric diagnoses known to be related to EF (ADHD, autism) were excluded because these children often get special help at school and/or medication to enhance EF.

Parents gave their written informed consent prior to study participation. Both studies were approved by central and local Institutional Review Boards prior to implementation of any study procedures.

Measures

Demographic and Diabetes-Related Characteristics

Hemoglobin A1c (HbA1c) closest to the time of assessment (spanning 3 months before or after questionnaire completion), and diabetes duration were retrieved from medical charts. In Belgium and the Netherlands, continuity and quality of HbA1c results are guaranteed, as both countries have similar assays to measure HbA1c, and follow the NGSP HbA1c standardization program (33).

Externalizing behavior

Externalizing behavior was measured using the Strengths and Difficulties questionnaire (SDQ; parent version) (34). SDQ captures emotional and behavioral functioning and contains 25 items, rated on a 3-point Likert scale. For the current study, we used the Externalizing Problems subscale, consisting of conduct problems and hyperactivity/inattention (range 0-20, higher scores indicating more problems). According to the age of their child, parents were provided with the age-appropriate version of the questionnaire was 0.78 in the current study.

Executive Function

Parents completed the Behavior Rating Inventory of Executive Functioning (BRIEF) to (24; 35). This 75-item questionnaire assesses wheth

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certain behaviors on a 3-point Likert scale (never, sometimes, or often, scored as 1, 2, and 3, respectively). Higher scores indicate more EF problems. The questionnaire consists of the subscales of the Behavioral Regulation index (i.e., Inhibit, Shift, Emotional Control) and the Metacognition index (i.e., Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor). Examples of questions are regulation), and

child

(metacognition). For a complete description of the eight subscales, we refer to Goia et al., 2002 (24) and Roth et al., 2014 (35). In this study, we found high internal consistency of both the

Statistical analyses

First, exploratory bivariate Pearson correlations between variables were calculated. Second, to examine whether there was a relationship between externalizing behavior and HbA1c, and whether this relationship was mediated by the two EF subdomains (i.e., metacognition and behavioral regulation), two separate bootstrap mediation analysis for mediation through the Process Macro were applied (36), correcting for age, illness duration, and sex, based upon their known predictive value and clinical relevance for glycemic control. A p value of $<.05$ was considered statistically significant. Third, we then performed post-hoc analyses with the subscales of the mediator that was found to be statistically significant to gain insight into which specific domains contributed to the mediation. All mediation analyses were performed with a bootstrap of 5000 resamples, in which random samples based on the original data are generated. A 95% Bias Corrected and Accelerated confidence interval (BCa) was calculated. We used SPSS v26 to perform the analyses.

RESULTS

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Sample characteristics

A total of 335 parents of 335 unique children and adolescents (6-18 years) with T1D completed the questionnaires (Belgium N=161; The Netherlands N=174; 88% mothers). Mean age was 12.3 ± 2.8 years, duration was 5.3 ± 3.6 years and mean HbA1c was $7.6 \pm 1.1\%$ (60 ± 12.0 mmol/mol). Characteristics of the sample can be found in Table 1.

Correlation and Mediation Analyses

First, as shown in Table 2, exploratory correlations revealed that the association between SDQ Externalizing Problem Behavior and HbA1c was significant ($r=.19$, $p<.001$), with more parent-reported child externalizing behavior associated with higher HbA1c. The association between the BRIEF Behavioral Regulation index and HbA1c was not significant ($r=.07$, $p=.23$), while the BRIEF Metacognition index was significantly associated with HbA1c ($r=.27$, $p<.001$). Further, SDQ Externalizing Problem behavior was significantly associated with both indexes of the BRIEF (Behavior Regulation $r=.65$, Metacognition $r=.67$, respectively; both $p<.001$).

Second, as depicted in Figure 1, subsequent mediation analysis confirmed that the mediation model of the associations between SDQ Externalizing Problem Behavior and HbA1c was significant. A significant total effect (c-path) was found between Externalizing Problem Behavior and HbA1c ($b = 0.06$, $p<.001$), indicating that higher SDQ Externalizing Problem Behavior scores were associated with higher HbA1c values. Mediation analysis showed that this relationship was mediated by metacognition as the indirect effect was significant (ab path point estimate = 0.05, BCa 95% 0.02 to 0.08) and the direct effect (c' path) was not significant anymore ($b = 0.01$, $p = 0.63$). This mediation effect indicates that increased externalizing problem behavior was associated with more problems in the metacognition domain (a path $b = 3.2$, $p < 0.01$) and more metacognition problems were associated with higher HbA1c values (b path $b =$

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.02, $p < 0.01$). The model explained 13% of the variance ($p < 0.001$). Lastly, no mediation was found of behavioral regulation in the relation between externalizing problem behavior and HbA1c.

Third, post-hoc analyses with the individual subscales of the Metacognition index showed that the mediation was significant for the subscales Initiate, Plan & Organize and Working memory (Figure S1), and not for Organization of materials and Monitor. Results for the mediation analyses for these subscales can be found as online supplementary figures.

DISCUSSION

To our knowledge, our study is the first cross-national study joining two EU databases from multicenter studies to examine the role of externalizing behavior and mediator executive function (EF; metacognition and behavioral regulation) in the complex pathway to glycemic control. In joining our two databases, we included a relatively large sample of parents reporting on children and adolescents with T1D in a wide age range (6-18 years).

As expected, externalizing behavior was positively associated with glycemic control more parent-reported child externalizing behavior was linked to higher HbA1c, a finding that is in line with previous research linking externalizing behavior to worse diabetes outcomes (12; 37). With regard to EF, more parent-reported problems in the metacognition domain (i.e., ability to plan and organize, monitor behavior, and use working memory) were related to higher child HbA1c. This is not surprising, given the important role of competencies such as planning, shifting of attention etc., for diabetes self-management. However, the lack of association between behavioral regulation (i.e., the ability to control impulses, and to regulate emotional responses appropriately) and glycemic control in our study, is somewhat surprising, and in contrast to - albeit few- earlier research in youth with T1D (21; 31). Further, externalizing behavior was significantly associated with both behavioral regulation and metacognition, which is in line with

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research in the general population linking externalizing behavior to worse EF (27; 38). Moreover, a recent neuro-imaging study (39) in youth with T1D found a link between more brain activation during an inhibitory control task (with inhibition being a part of behavioral regulation) and fewer conduct problems.

In line with our hypothesis, metacognition was found to mediate the relationship between externalizing behavior and glycemic control, indicating that this specific subdomain of EF needs to be taken into account when a child or adolescent displays externalizing behavior that may impact upon glycemic control. Indeed, not surprisingly, subsequent post-hoc analyses with the individual subscales of the Metacognition index indicated the particular significant relevance of abilities such as planning and organizing, initiating activities, and working memory (i.e., the ability to hold information when completing a task) as mediators between externalizing behavior and glycemic control. In line with conclusions of Sulik et al. in the general population (26), our findings may point to the fact that those children and adolescents displaying stronger EF, may be better at organizing and planning, and at taking into account possible negative consequences of their behavior. These specific competencies could then buffer the negative effects of externalizing behavior in the pathway towards glycemic control. In turn, the reverse pathway could also be possible externalizing behavior, and the associated emotions, could also interfere with children's ability to effectively deploy EF, perhaps slowing its development over time (40; 41). Indeed, such associations may well be bidirectional (42). In contrast to findings with regard to metacognition, and against expectations, subdomain behavioral regulation (i.e., the ability to control impulses, and to regulate emotional responses appropriately) did not seem to function as a mediator in the link between externalizing behavior and glycemic control. As mentioned above, our data suggest that more parent-reported child externalizing behavior is related to more parent-reported child behavior regulation problems. However, in our study, parent-reported child

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behavioral regulation is not associated with HbA1c, and does not explain the relationship of externalizing behavior and glycemic control. This is surprising, especially given previous findings linking behavioral regulation to diabetes-related outcomes such as self-management and glycemic control (21; 30). The interplay between variables affecting glycemic control is complex and changing over time when children grow up. Although the wide age range of our sample adds value to current research, and despite the fact that we corrected for age in the analyses, EF as well as self-management skills are under development from childhood into late adolescence. It might be that specific EF problems affect different aspects of self-management and glycemic control at different ages, affecting the associations and mediation we studied in the current research. Furthermore, previous research has shown that diabetes self-management seems to mediate the relationship between EF and HbA1c (43). Hence, it could be that findings would be different with diabetes self-management rather than glycemic control as outcome. In this context we also have to keep in mind that diabetes care is a family affair in this age group and parental factors should be taken into account as well. With the transition of self-management tasks from parents to (44), the division of the responsibilities for these tasks as well as parental EF are important factors to consider in research and clinical care (19; 20).

In sum, our findings point to the importance of taking into account the validity of the specific metacognition-related skills such as planning and organizing, initiating activities, and working memory, that are highly related to diabetes self-management. For example, youth with T1D, and -given future replication of our findings- most specifically those who display externalizing behavior, need to acquire the ability to initiate optimal self-management strategies and generate ideas, and necessitate the ability to anticipate future events, set goals (planning and

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organizing), and the cognitive skills to hold information when sequentially performing plans (working memory).

Clinical Implications

Several implications for clinical practice can be derived from this research. First, in line with previous research (7; 45; 46) (52) we suggest integrating neurocognitive and behavioral screening into routine diabetes care for children and adolescents with T1D. Although externalizing behavior problems are readily identifiable in clinical practice, and although this as well as previous research (12) demonstrates a detrimental association with glycemic control, assessment of this risk factor seems underrepresented in clinical practice. The same goes for screening for EF problems, despite mounting evidence of the detrimental effect of EF problems on diabetes self-management and glycemic control. Second, beyond the suggestion of screening, a more preventive approach in clinical practice may be wise. Specifically, it would be meaningful to make members of the multidisciplinary diabetes team aware of the importance of further assessment of strengths and weaknesses in the EF domain, when more readily identifiable difficulties with regard to externalizing behaviors arise. For example, in the presence of such difficulties, clinicians may focus with the child/adolescent on the externalizing behavior problems, as well as on the more EF related issues such as planning and organizing of diabetes self-management tasks, especially as research is beginning to show that EFs may be trainable in at-risk youth (e.g., (47-49)). Hence, in line with previous research linking EFs to longitudinal change in externalizing behavior (50), targeting EF may be an effective approach to reduce the indirect impact externalizing behavior may have on glycemic control in children and adolescents with T1D. Ecological momentary assessment (EMA) techniques with personalized biobehavioral feedback may also be a future avenue for clinical implementation in busy clinics (51). In addition

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to the beneficial effect of feedback, EMA may also make identification of adolescents at risk, and in need of more specialized intervention more feasible.

Limitations and suggestions for future research

EF and externalizing behavior problems have been identified as multi-dimensional constructs, and even in the abundance of research on these variables in the general population, much remains unclear about their specific association (26). To our knowledge, our study is the first to investigate this association in children and adolescents with T1D. Although our study helps to unravel the complex pathways between externalizing behavior problems, EF, and diabetes outcomes, several limitations need to be acknowledged. First, due to the cross-sectional study design, causality cannot be inferred. Future longitudinal research is needed to dive deeper into the underlying mechanisms and dynamic directionality of the associations between externalizing behavior problems, EF, and glycemic control. Second, in the Belgian sample, children with psychiatric disorders affecting EF such as ADHD were excluded because these children often get special help at school and/or medication to enhance EF. Although the total number of participants in the current study (Belgian and Dutch data combined, N=336) is relatively large, this exclusion could have slightly impacted results. It may be valuable for future research to include this subgroup of children and adolescents, as the co-occurrence of T1D with certain psychiatric diagnoses may impose additional challenges to self-management. Third, although the BRIEF is still considered the gold standard to assess EF by means of a questionnaire (25) due to its ecological validity, there may be a need to rethink the utility of such a broad and non-diabetes-specific measure. For example, performance-based measures, diabetes-related measures of EF, and ecological momentary assessment may be valuable additional approaches to screening and research (18; 21; 51-53). Fourth, this research has been done in two European countries and significant differences in HbA1c have been identified between the US and the EU,

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(4). Hence, external

countries outside the EU may be difficult, as, for example, HbA1c generally tends to be higher in the US as compared to the EU. Fifth, given that pubertal status and timing may potentially be associated with EF and externalizing behavior, future research may benefit from including these variables as well (32). Lastly, based on research in the general population we can expect some degree of overlap and association between specific aspects of EF, and specific aspects of externalizing behavior, that may account for some of the associations (e.g., child self-regulation a concept closely related to behavioral regulation, and attention-related problems; (54)). It may be worthwhile to further examine this overlap in future research.

To conclude, this cross-national collaboration combining two cohorts from Belgium and the Netherlands helps to unravel the role of EF in the complex interplay between externalizing behavior and glycemic outcomes. To quote Sulik & Obradovic (26) who reported on the

still unknown

Therefore, we make a call for future research to investigate this dynamic between two variables of impact on glycemic outcomes in adolescents with T1D, and in doing so, to join forces, not only within but also across continents.

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Table 1. Sample characteristics

	N=335
Sex (Female) %	49.6
Age	12.3 (2.8)
Diabetes duration	5.3 (3.6)
Treatment (pump) %	52.5
HbA1c	7.6 % (1.1) / 60 mmol/mol (12.0) Range 5.0-11.6
SDQ externalizing problems	4.2 (3.5) Range 0.0-16.0
BRIEF Behavioral regulation	41.3 (9.9) Range 28.0-77.0
BRIEF Metacognition	74.6 (17.1) Range 44.0-121.0

Data are mean (sd) unless otherwise indicated

Table 2. Pearson correlations of the variables of interest

	SDQ Externalizing Problem Behavior	BRIEF Behavioral Regulation	BRIEF Metacognition	HbA1c
SDQ Externalizing Problem Behavior	1	.65***	.67***	.19***
BRIEF Behavior Regulation		1	.63***	.07

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BRIEF Metacognition			1	.27***
HbA1c				1

*p **p ***p

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Graphical representation of the mediation model

123x85mm (300 x 300 DPI)

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