

Nutritional Status of Underprivileged Indian Children and Youth with Type-1 Diabetes - A Multicentre Study

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Abstract

Background: India has the highest number of prevalent type-1 diabetes (T1D) cases in the under-20-year age population. Data on the anthropometry of underprivileged Indian children with T1D are scarce. In economically disadvantaged countries like India, poor growth in patients with T1D is a major concern due to limited accessibility and affordability. Besides, due to the double burden of malnutrition, the prevalence of obesity is increasing mirroring the global trends, which may lead to the development of insulin resistance. **Objectives:** This study aims to assess the prevalence of malnutrition in Indian children and youth with T1D and to identify the determinants of short stature. **Methods:** A registry-based cross-sectional analysis of data collected from various centres across India enrolled in the Changing Diabetes in Children (CDiC) programme. **Results:** We observed that 6.4% were undernourished (3.4% severe undernutrition) and 17.7% (overweight 13.2%) had combined overweight/obesity. 21.2% of participants had short stature (adjusted for mid-parental height) with 7.4% cases of familial short stature. Longer duration of illness and insulin requirement were significant positive predictors of short stature while glycaemic control, insulin regimen and mid-parental height did not have a significant relationship with short stature. Participants on basal-bolus regimen had significantly higher insulin requirements and better glycaemic control than the ones on mixed-split regimen. **Conclusion:** We report that around one-fifth of children and youth with T1D were overweight/obese and around a fourth were stunted, especially those with longer duration of diabetes and higher insulin requirements. Close monitoring of anthropometric parameters is necessary for all children with T1D to optimize growth and nutrition.

Keywords: India, multicentre, obesity, stunting, type-1 diabetes, undernutrition

INTRODUCTION

Type-1 diabetes (T1D) is caused by the autoimmune destruction of insulin-producing β -cells of the pancreas as a result of genetic susceptibility and environmental triggers leading to insulin deficiency. It is one of the most common chronic disorders of childhood and occurs more frequently in children and young adults. The 10th edition of the International Diabetes Federation (IDF) atlas published in 2021, reports that India has the highest estimated number of prevalent T1D cases in children and youth under 20 years of age (229,400). It also has the highest estimated number of new cases of T1D in children and adolescents per annum (24,000).^[1]

It is well known that abnormalities in the hypothalamic-pituitary-growth hormone axis are noted in patients with T1D as insulin is a major regulator of the growth

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hormone/insulin-like growth factor (GH/IGF) axis.^[2] Insulin regulates the expression of hepatic GH receptors and affects IGFs and IGF-binding protein (IGFBP) synthesis by modulating GH post-receptor events. As low levels of portal insulin are noted in children with T1D, there is GH hypersecretion, low circulating IGF-I and IGFBP-3 and high circulating IGFBP-1 levels resulting in poor growth.^[2] Moreover, the management of T1D is often rendered difficult as it comprises regular daily insulin use, frequent blood glucose monitoring, optimum physical activity and a healthy diet which is especially difficult to follow in early childhood and adolescence even in countries with access to healthcare facilities. All these factors have a significant effect on the growth of these children. Reports suggest that the impact of T1D on growth is not significantly relevant in developed countries due to more physiological insulin substitutions and regular self-monitoring. However, in economically disadvantaged countries like India where access to insulin and other self-care tools is limited, usage of conventional regimes by a vast majority of patients causes underinsulinization and suboptimal metabolic control along with factors like low socioeconomic status, poor family support, emotional issues and poor compliance ultimately leading to poor growth.^[3] An Indian study has shown that children on intensive therapy (basal-bolus) had a higher height Z-score and better glycaemic control than the children on conventional therapy (mixed-split), though the difference was not significant.^[2]

The 2021 Global Nutrition Report pictorially depicts the trend of the nutrition status of Indian children and adolescents (<https://globalnutritionreport.org/resources/nutrition-profiles/asia/southern-asia/india>).^[4] There is an increase in the 'double burden' of malnutrition in low- and middle-income (LMIC) countries like India due to nutritional transition, economic growth, urbanization and lifestyle changes like poor diet and reduced physical activity; global health targets have thus shifted focus to all forms of malnutrition which include overweight and obesity.^[5] The double burden of malnutrition is characterized by the coexistence of undernutrition along with overweight and obesity or diet-related non-communicable diseases, within individuals, households and populations, and across the life-course.^[6] Globally, the prevalence of overweight/obesity in the paediatric population has increased from 4% in 1975 to 18% in 2016. Mirroring the global increase in obesity prevalence, the number of obese patients with T1D is also increasing.^[7] Adiposity is a major factor causing insulin resistance (IR) leading to increased insulin requirement, which in turn may result in insulin-induced weight gain. The proposed mechanism for these events is the reduction of blood glucose level concentrations below the renal threshold, increasing calorie intake due to the fear of hypoglycaemia or unphysiological metabolism of insulin followed by subcutaneous administration.^[8,9] The burden of these two concurrent health problems (obesity and T1D) may have notable implications for both patients and their families.

In India, health has improved in recent decades, but undernutrition disproportionately burdens the poor especially

the urban poor due to low-quality of public service provisions such as access to water, sanitation, decent housing and health insurance.^[10] However, the combined prevalence of overweight/obesity has increased from 15.9% before 2001 to 19.3% after 2010.^[11] As data on anthropometric parameters in underprivileged Indian children with T1D on conventional insulin versus intensive insulin therapy are scarce, we conducted this multicentre study with the objective to assess the prevalence of malnutrition (undernutrition [including short stature] and overnutrition) in Indian children and youth with T1D and to identify the determinants of short stature.

METHODS

Changing Diabetes[®] in Children (CDiC) is a programme aimed to provide comprehensive and sustainable diabetes care to children and young adults with diabetes hailing from economically challenged families. It was established in India in September 2011 to provide comprehensive care and life-saving medications for children with T1D and to safeguard a healthy future for them, for whom diabetes care is not always available or accessible. The key benefits, namely, medication, monitoring, diagnostics consultation and self-management of diabetes for each child registered in the programme are highlighted in Figure 1. Children with T1D belonging to the economically weaker sections of society supported by a Below Poverty Line (BPL) card and/or verified by the participating investigators were included in the programme. Children and parents were free to withdraw from the programme at any given point in time without giving any reason. A registry with data related to the participating children under the custody of respective centres with access only to the treating doctor is in place. Ethics approval has been obtained from the Ethics Review Board of all the institutions participating in the CDiC programme. The details of the programme through the patient information sheet (PIS) were shared with all participants and their parents and written informed consent (ICF) for their voluntary participation was obtained. The treating doctors in all participating centres have exclusive access to the CDiC web portal for their own centres and are trained for data entry. Each centre keeps a log for the identification of patients and all data are anonymously stored in the CDiC portal. The latest data collected by centre coordinators (before extraction) which were related to growth were analysed from nine CDiC centres. Data were extracted in September 2021.

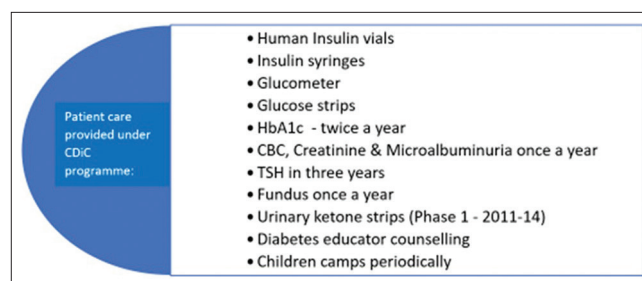


Figure 1: Key components of patient care under CDiC programme

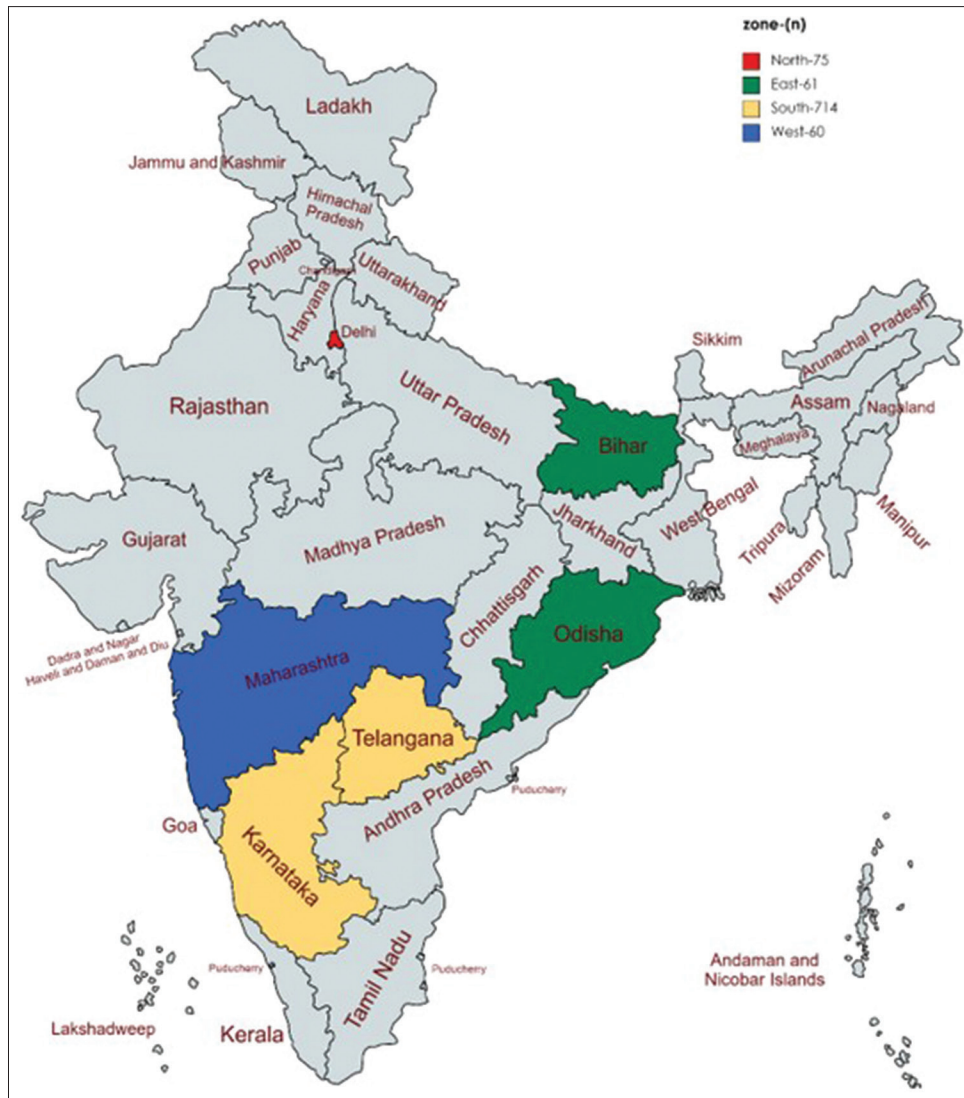


Figure 2: Classification of participants with T1D based on BMI categories

Design

This study is a registry-based cross-sectional analysis of data collected, including patients across India, enrolled in the CDiC programme.^[12]

Descriptive data

For each patient, the data from the most recent visit (before data extraction) were analysed. Children and youth with comorbidities like celiac disease, renal tubular acidosis (RTA), Cushing disease and haemolytic anaemia and those with other causes of short stature like a history of drug intake including antiretroviral drugs and antioxidants, chemotherapy, radiotherapy, etc., were excluded from the study. Height, weight and body mass index (BMI) were converted to Z-scores using Indian reference data; participants with age >18 years were considered to have attained adult height.^[13] Treatment modalities were divided into two groups: mixed-split regimen: 0–3 injections/day and basal-bolus regimen: 4–5 injections/day.

Glycaemic control was assessed by glycated haemoglobin concentrations (HbA1c), which were measured locally at each centre. The American Diabetes Association (ADA) has suggested the following target values for HbA1c in relation to age: <8.0% at age 6–12 years, <7.5% at age 13–18 years and <7.0% at age 19+ years. Individuals who met the ADA target were classified as ‘good’ control; those with HbA1c $\geq 9.5\%$ regardless of age were classified as ‘poor’ control; and those with HbA1c values between the definition of ‘good’ and ‘poor’ control were classified as ‘intermediate’ control.^[14]

Four geographic regions were defined as North: Delhi and National Capital Region (NCR), South: Bengaluru, Hyderabad, West: Mumbai, Pune, East: Patna, Bhubaneshwar.^[15]

Statistical analysis

All statistical analyses were carried out using the SPSS for Windows software programme, version 26 (SPSS, Chicago, IL, USA). All outcome variables were tested for normality

before performing statistical analyses. Differences in means were tested using Student's t-test for parametric data, Mann–Whitney U test for non-parametric data and Chi-square test for categorical variables. For testing relationships between dichotomous-dependent variables and continuous predictors, binary logistic regression analysis was carried out. The dependent variable in the model was the presence or absence of short stature while the independent variables were duration of illness, insulin requirement, insulin therapy regimen, glycaemic control and mid-parental height. *P* values <0.05 were considered as statistically significant.

Ethical clearance statement

The study was approved by the institutional ethics committee named as 'Ethics Committee, Jehangir Clinical Development Center Pvt Ltd.' vide letter no NA (our ethics committee does not provide an approval number) on 4th March 2022. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures follow the guidelines laid down in Declaration of Helsinki 2008.

RESULTS

A total of 910 children and young adults (75 from North, 61 from East, 714 from South and 60 from Western India) with T1D as shown in Figure 3 were studied. Of these, 427 (46.9%) were boys and 483 (53.1%) were girls. The participants in the study were in the age range of 4–25 years with a mean age of 16.1 ± 4.5 years. The mean age at the onset of diabetes and duration of illness were 7.8 ± 3.9 years and 8.2 ± 4.0 years, respectively. Amongst associated comorbidities known to co-exist with T1D, hypothyroidism was observed in 33 (3.6%) subjects while 44 subjects (4.8%) developed diabetic nephropathy as a complication. The mean insulin requirement and HbA1c were 1.1 ± 0.4 U/kg/day and 10.2 ± 1.7 g, respectively. Amongst the 910 subjects started on insulin therapy, 703 (77.3%) were on a mixed-split regimen while 207 (22.7%) were on a basal-bolus regimen. We also observed that 14.8% of subjects had delayed onset of puberty (the first sign of puberty >13 in girls and >14 in boys). With respect to compliance, 47.5% of participants had good compliance for insulin administration (based on the number of insulin injections administered if <2 in the mixed-split and <4 in basal-bolus). Moreover, compliance with pre-meal blood glucose monitoring was poor with an average of around 32.6% of subjects measuring glucose less than once a day.

Since study subjects were on mixed-split and basal-bolus regimens, anthropometric and other parameters have been described for the two groups separately. As seen in Table 1, participants on basal-bolus regimen were older with older age at onset, had higher insulin requirements and better glycaemic control ($p < 0.05$). There was no significant difference in anthropometric parameters of the subjects including adult height achieved in the older subjects.

We report a prevalence of undernutrition of 6.4% (including 3.4% severe undernutrition) based on BMI categories in our study population. The prevalence of combined overweight and obesity in our study population was 17.7% (overweight 13.2% and obese 4.5%). The classification of participants based on BMI categories is shown in Figure 2. There was no significant difference in the proportion of overweight/obesity based on the regimen of insulin administration ($p > 0.05$). The overweight/obese subjects were significantly older and had a higher duration of diabetes and had significantly higher insulin requirements. However, they had better glycaemic control than non-overweight subjects ($p < 0.05$).

We found that 261 (28.7%) subjects with T1D had height Z-score <-2 SD. Of these, 68 (26% of short subjects, 7.4% overall) subjects had height in the mid-parental range of 1.5 SD thereby suggesting they had familial short stature. Thus, around 193 (21.2%) children had short stature after adjusting for mid-parental height. Subjects with height Z-score <-2 SD had a significantly higher duration of diabetes and higher insulin requirement with younger age at onset ($p < 0.05$).

Binary logistic regression analysis was performed to predict the occurrence of short stature in subjects with T1D with the dependent variable as the presence or absence of short stature (height Z-score <-2). The independent variables used to predict short stature were duration of illness, insulin requirement, insulin therapy regimen, glycaemic control and mid-parental height. Binary logistic regression analysis showed that the duration of illness and insulin requirement were significant positive predictors of short stature. Glycaemic control, insulin regimen and mid-parental height did not have a statistically significant relationship with short stature. The model inclusive of all risk factors was significant ($p < 0.05$) with Nagelkerke R^2 of 0.122 and a correct prediction percentage of 76.7% as seen in Table 2.

DISCUSSION

In our multicentre study on subjects with T1D who had poor glycaemic control as judged by mean HbA1c and had inadequate blood glucose monitoring with a majority of children being on a mixed-split regimen, we observed that 6.4% were undernourished (including 3.4% severe undernutrition) and 17.7% (overweight 13.2% and obese 4.5%) had combined overweight/obesity. 21.2% of participants had short stature (adjusted for mid-parental height) of which 7.4%

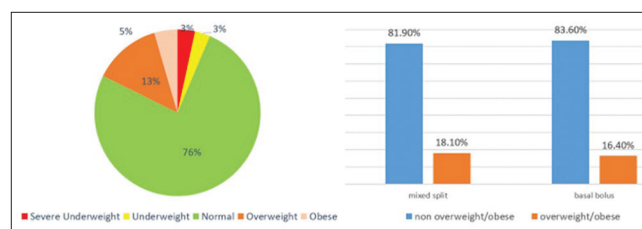


Figure 3: Number of participants of T1D enrolled in CDIC based on geographic regions

Table 1: Comparison of demographic, anthropometric and laboratory parameters between study participants based on an insulin regimen

Parameter	Mixed-Split (n=703)		Basal-Bolus (n=207)		Significance
	Mean	SD	Mean	SD	
Age of patient (years)*	15.7	4.5	17.2	4.0	<0.01
Age of onset (years)*	7.5	3.7	8.8	4.1	<0.01
Duration of illness	8.2	4.1	8.3	4.0	0.541
Height Z-score	-1.3	1.4	-1.2	1.9	0.06
% Short Stature	27.3%		33.3%		
Weight Z-score	-0.7	1.3	-0.7	1.7	0.2
BMI Z-score	-0.3	1.4	-0.4	1.2	0.205
% Overweight/Obese	18.1%		16.4%		
Adult height Z-score (n=397)	-1.1	1.5	-1.5	1.5	0.138
Difference between height Z-score and MPH Z-score	0.9	1.6	1	1.6	0.4
Insulin requirement (U/kg/day)*	1.1	0.4	1.3	0.6	<0.01
TSH milli IU/ml	2.16	1.38	2.37	1.28	0.322
ACR mg/g	17.8	25.0	28.1	36.4	0.688
HbA1c* g%	10.3	1.7	10.0	1.7	0.05

SD - Standard deviation, BMI - Body mass index, MPH - Mid-parental height, ACR - Albumin creatinine ratio, HbA1c - Glycated haemoglobin

Table 2: Variables in the equation of binary logistic regression for short stature

Parameter	B	SE	Wald	Df	Sig	Exp (B)
Duration of illness	0.077	0.038	4.217	1	0.04	1.08
Insulin requirement	1.475	0.455	10.499	1	0.001	4.37
Regimen (1)	0.197	0.345	0.326	1	0.568	1.218
Mid-parental height Z-score	-0.282	0.151	3.49	1	0.062	0.754
Glycaemic control (1)	0.53	0.365	2.109	1	0.146	1.699
Constant	-4.061	0.818	24.664	1	0	0.017

were cases of familial short stature. Longer duration of illness and insulin requirement were significant positive predictors of short stature while glycaemic control, insulin regimen and mid-parental height did not have a statistically significant relationship with short stature. Moreover, participants on the basal-bolus regimen had significantly higher insulin requirements and better glycaemic control than the ones on the mixed-split regimen.

A systematic review of the epidemiology of childhood overweight and obesity in India reported a 19.3% prevalence of combined overweight/obesity in Indian children and adolescents.^[11] Another Indian cross-sectional, multicentric study on children and adolescents reports a 19.1% prevalence of overweight/obesity as judged by ethnic-specific (Indian Academy of Pediatrics, IAP) cut-offs.^[16] Hence, the prevalence of overweight/obesity in Indian children and adolescents with T1D (17.7%) was similar to the general population of children and youth in India. Another Indian study has also reported a combined prevalence of overweight/obesity of 15.5% in subjects with T1D.^[8] Studies from other countries like Turkey (18%), Poland (30.2%) and Israel (24.2%) also report a similar prevalence of overweight/obesity in children with T1D as in non-diabetic children.^[7,17,18] The SEARCH for

Diabetes in Youth (SEARCH) study also reports 34% prevalence of combined overweight/obesity in T1D similar to non-diabetic American youth (33%).^[19] We also report overweight/obese subjects with T1D had longer duration of illness and higher insulin requirement but also had better glycaemic control. Thus, intense insulin therapy due to anabolizing and lipogenic effects of insulin, change in eating habits and shift to a sedentary life style may be some reasons for a worldwide increase in combined overweight/obesity in children and adolescents with T1D, thus mirroring the global trend.

We report a 6.4% prevalence of undernutrition in our study. This is similar to the 5% reported by a Polish study conducted on children with T1D. The same study found a similar prevalence in otherwise healthy children without diabetes.^[20] In contrast to our study, a Turkish study found that 21 out of 72 study participants (29.1%) had BMI less than the 10th percentile.^[21] Similarly, a study from Iraq has reported a 19.7% prevalence of undernutrition in children with T1D which was much higher than in non-diabetic subjects (2.44%).^[22] Single-centre studies in children with T1DM from India (13.2%) and Croatia have also reported a higher prevalence of undernutrition.^[2,23]

A review on the double burden of malnutrition in Indian children who did not have T1DM reports a prevalence of thinness ranging from 5.5% to 53.9%.^[24] A recent report has estimated a 26.7% prevalence of thinness in Indian adolescents.^[25] Evidence from large-scale surveys to determine the double burden of malnutrition has reported an overall 24.8% prevalence of thinness in Indian adolescents.^[26] We found a significantly lower prevalence of undernutrition in patients with T1D than in other Indian studies which may be attributed to single centre analysis and smaller sample size in those studies. In comparison to the general population, the prevalence may be lower in subjects with T1D due to weight

gain due to the anabolic effects of insulin therapy as well as the difference in criteria used to classify BMI.

Similar to our findings (we found short stature in 21.2% of children and youth with T1D), Khadilkar *et al.*^[2] also report that 27.1% of subjects with T1D had height Z-score <-2 SD. Another study from south India reports a 27% prevalence of short stature in subjects with T1D.^[27] Studies from Rwanda and Iraq have reported a 30.9% and 15% prevalence of stunting in children with T1D, respectively.^[28,19] On binary logistic regression analysis, we identified the duration of illness and insulin requirement as significant predictors of short stature. A study on longitudinal growth in children and adolescents with T1D also identified the duration of illness as a significant predictor of short stature.^[29] Various studies including ours did not find a significant effect of glycaemic control on growth in subjects with T1D.^[2] Dysregulation of the GH/IGF-1 axis in T1D with a decrease in IGF-1, IGFBP3, and an increase in GH binding protein possibly affects the growth plate and results in stunting. Other possible causes include poor glycaemic control, concomitant thyroid illness, compromised renal function and psychosocial factors.^[3] However, a multicentre study from Europe has suggested that subjects receiving modern diabetes treatment are taller than expected. They also concluded that major growth disturbances are limited and special attention should be directed towards children with a younger age at onset (hence the longer duration of illness), obesity, higher HbA1c and poor compliance to optimize growth.^[30]

To the best of our knowledge, this is the first multicentre study from the Indian subcontinent to assess the nutritional status of children and youth with T1D. Lack of longitudinal follow-up, dietary history, pubertal status and body composition parameters are the limitations of our study. Depending upon the methodology, HbA1C may be altered in patients with haemoglobin variants, which was not assessed in this study. Also, although there were no differences in the mean anthropometric parameters between regions (data not presented), the number of patients with T1D was much more from the Southern region.

In conclusion, we report that around one-fifth of the children and youth with T1D were overweight/obese, and around a fourth were stunted, especially those with a longer duration of diabetes and higher insulin requirements. Thus, close monitoring of anthropometric parameters is necessary for all children with T1D to optimize growth and nutrition.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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