Original Article
PEDIATRIC OBESITY

Obesity

Association Between Paracetamol Use in Infancy or Childhood with Body Mass Index

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Objective: Paracetamol has the potential to also promote weight gain by indirect activation of cannabinoid receptors. The association between paracetamol use in the first 12 months of life or recent high use and BMI in children and adolescents was investigated.

Methods: Paracetamol use in the first 12 months of life (reported by parents/guardians of 6- and 7-year-olds) or in the past 12 months (reported by parents/guardians of 6- and 7-year-olds or self-reported by adolescents aged 13–14) was examined in relation to BMI in a large multicentre cross-sectional study (2000–2003). Linear regression results were adjusted for whether height and weight were reported or measured, age, sex, country gross national income, study centre, maternal smoking, and recent wheeze.

Results: Data were available from 76,216 children (18 countries) and 188,469 adolescents (35 countries). BMI was +0.07 kg/m^2 higher in children with early life paracetamol exposure, from affluent countries only. Frequent recent paracetamol use was associated with higher BMI (+0.17 kg/m^2, $P < 0.0001$) among adolescents from affluent countries only, but not in children ($P = 0.41$).

Conclusions: Paracetamol may be causally related to increased BMI; alternatively, the association may be explained by lifestyle or other factors that correlate with paracetamol use in affluent countries.

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Introduction

Paracetamol is the most commonly used analgesic and antipyretic used in children (1,2); however, its primary site of action is unclear (3,4). Experimental data demonstrating that the analgesic effect of paracetamol is primarily due to the indirect activation of cannabinoid CB1 receptors has been reported previously by two independent groups (5,6). Paracetamol (also termed acetaminophen) refers to the compound para-acetyl-aminophenol or acetyl-para-aminophenol (APAP), which undergoes de-acetylation to para-aminophenol. After conjugation with arachidonic acid, it forms *N*-arachidonoylphenolamine (also known as AM404), which is a recognized endogenous cannabinoid (5). Furthermore, cannabinoid receptor type 1 (CB1) antagonists completely prevent the analgesic activity of paracetamol (6). In contrast to the AM404 hypothesis, an alternative mechanism of action of paracetamol is thought to be through inhibition of the synthesis of prostaglandins from arachidonic acid under specific conditions (7). However, this is also thought to impact on the cannabinoid system by reducing its oxidation (7).

Activation of cannabinoid receptors by paracetamol has the potential to promote weight gain. Several animal studies have highlighted the important role of cannabinoid receptor activation in the hypothalamus and limbic system in promoting hunger, food intake, and body weight [reviewed in (8)]. Genetic ablation of CB1 receptors in mice resulted in reduced body weight with reduction of food intake (9) even in a high-fat-diet environment (10). Selective cannabinoid receptor blockade by drugs such as rimonobant has been shown to decrease food intake and reduce body weight in humans (11-13),

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although neuropsychiatric side effects have limited its use as a weight loss agent (14). A modest effect of paracetamol on promoting appetite is difficult to ascertain from the numerous studies assessing its short-term safety and efficacy (as antipyretics and analgesics) in children (15-19).

Paracetamol is the most widely used analgesia in children. The frequency of use varies between countries. One international study reported more frequent recent use of analgesia for headache (approximately 50–60%) and stomach-ache (approximately 20–35%) in North American, the UK, Ireland, and Finland, while the prevalence among central European countries was below average, among 11- to 13-year-old children (20), although the specific medications used were not specified. A number of studies from Australia (21), Brazil (22), Germany (23), Denmark (24), UK (25), and the USA (26) have reported a tendency for increased use of analgesia by older children. There are fewer and conflicting reports of the prevalence of paracetamol use among children from less affluent countries such as Africa (27).

Given in the correct dosage, paracetamol use is considered a safe, "over the counter" analgesic and antipyretic agent. Overdose of paracetamol, whether accidental, inadvertent, or suicidal, can result in hepatic injury or even death (28). The effect of early life or cumulative postnatal paracetamol exposure on body mass index (BMI) in children has not previously been reported.

We investigated whether exposure to paracetamol in the first year of life was associated with higher BMI in childhood, and if there was a graded impact of subsequent paracetamol exposure on BMI among children participating in the large, International Study of Asthma and Allergies in Childhood (ISAAC). We took into account several factors which may confound this association by being related both to the propensity for early paracetamol use and current BMI: (a) maternal smoking during the first year of life and breastfeeding, both variably reported to be associated with offspring BMI, which may also affect early life paracetamol use through altering susceptibility to respiratory infections (29,30); (b) current wheeze, a marker of asthma which is both associated with increased BMI and may have caused respiratory symptoms in early life that may have led to increased paracetamol use (31); (c) gross national income (GNI), a marker of economic affluence of a country which may be associated with both increased BMI and receptivity to paracetamol use.

Methods

The ISAAC study is a multicentre, multicountry, cross-sectional study investigating the prevalence of the symptoms of asthma, rhinoconjunctivitis, and eczema and the role of risk factors and has previously been described (32). ISAAC Phase Three was undertaken from 2000 to 2003 and involved 6- and 7-year-old children and 13- and 14-year-old adolescents chosen from a random sample of schools in defined geographical areas. It used the Phase One Standardized Core Questionnaire on symptoms of asthma, rhinoconjunctivitis and eczema and included an optional environmental questionnaire (EQ) containing 28 questions to collect specific etiological data including height, weight, paracetamol use, and parental smoking. Parents or guardians completed questionnaires for those aged 6–7 years. Adolescents aged 13–14 years self-completed their questionnaires. The questionnaires were translated from English into the local language and then back-translated into English for verification (33).

The following two questions were asked from parents or guardians to ascertain paracetamol use among their 6- and 7-year-old children (isaac.auckland.ac.nz): in the first 12 months of your child's life, did you usually give paracetamol (e.g., Panadol, Pamol) for fever? Investigators were instructed to substitute locally appropriate brand names in the paracetamol questions to ensure that this was relevant for the local population. Parental responses were categorized as yes or no. In the past 12 months, how often on average have you given your child paracetamol (e.g., Panadol, Pamol)? Responses were never, at least once a year, or at least once per month, which were categorized as high (at least once per month) or low (both at least once a year or never) recent users of paracetamol respectively. Only the single question regarding paracetamol use during the past 12 months was asked of adolescents aged 13–14 years.

Breastfeeding, maternal smoking status, and current asthma symptoms were ascertained by the following questions directed to parents of 6- and 7-year-olds: Was your child breastfed? Did your child's mother (or female guardian) smoke cigarettes during your child's first year of life? Has your child had wheezing or whistling in the chest in the past 12 months? Adolescents aged 13–14 years old were asked: Did you have wheezing or whistling in the chest in the past 12 months? All these responses were categorized as yes or no. The questionnaires are available on the ISAAC website isaac.auckland.ac.nz.

Children's height and weight were reported by parents or adolescents, and in some centres height and weight were measured objectively (although there were no standardized or specific instructions for doing this). To eliminate likely erroneous data, those in the top and bottom 0.5% of weights and heights for each centre, and those with heights less than 1.0 m were excluded. Body mass index (BMI) was calculated [weight (kg)/height (m)^2] and all BMIs less than 9 kg/m^2 and greater than 40 kg/m^2 were removed (see Figure 1a). To be included in the analysis, centres had to have at least 70% complete paracetamol data. Individuals without complete age, sex, BMI, and paracetamol data were excluded.

The association between paracetamol use (either in the first year of life or used recently during childhood at 6–7 or 13–14 years of age) and individual childhood BMI was assessed using a general linear mixed model with sex within centre as the random effect, and fixed effects of age, sex, BMI measurement type (by parent-report or using objective measurement of height and weight) and paracetamol use. Further analyses were done including maternal smoking, breastfeeding, and current wheeze in the model. The interactions of paracetamol use with age, exposure to maternal smoking, breastfeeding, current asthma symptoms, and paracetamol administration (in the first 12 months of life) were examined. We tested for interactions with GNI of each country according to World Bank data by categorizing countries as nonaffluent (low or lower middle income) or affluent (upper middle or high income) (34). Analyses used SAS (v 9.3, SAS Institute, Cary, NC).

Results

A total of 76,216 children aged 6–7 years from 31 centres in 18 countries (13 affluent, 5 nonaffluent) contributed data on both

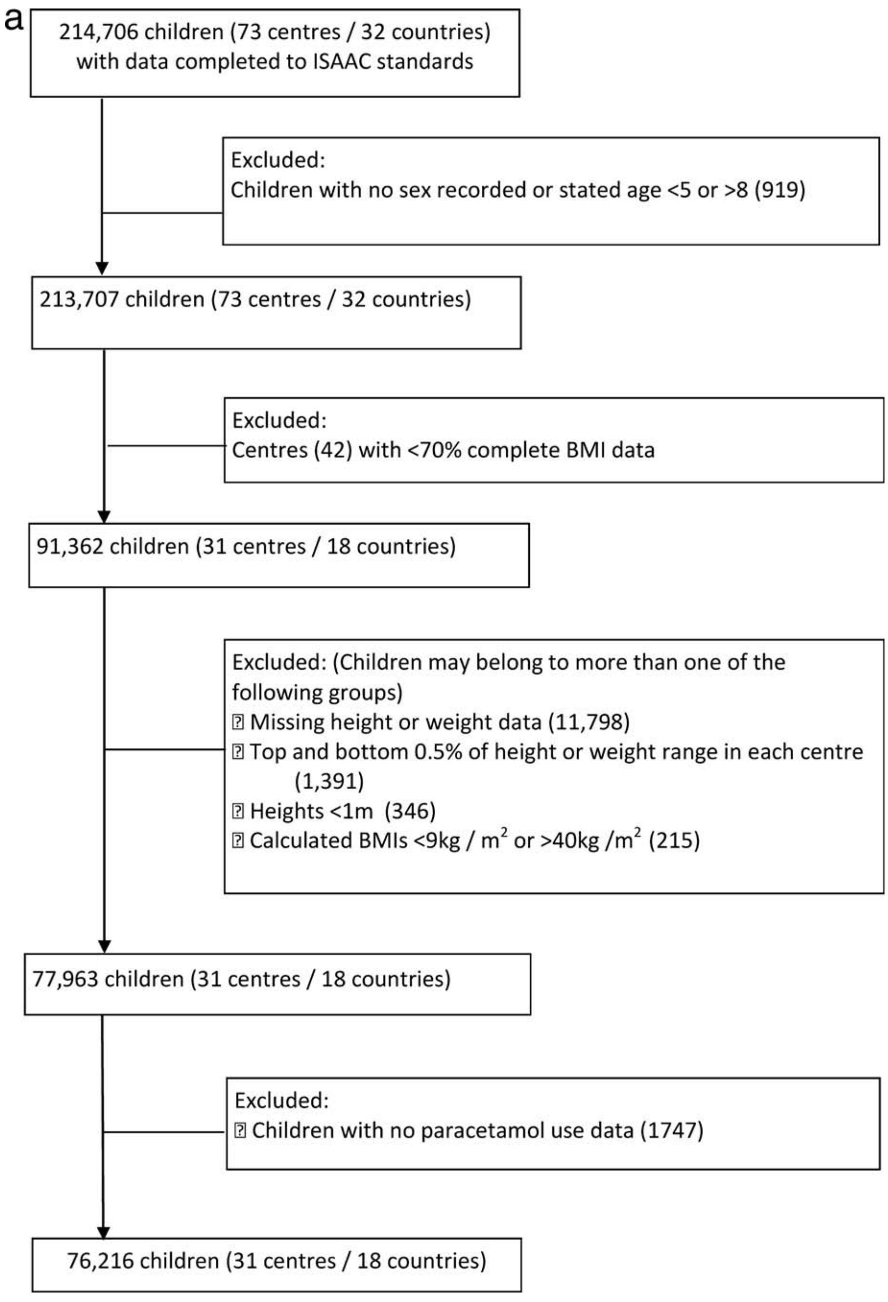

Figure 1 Flow of (**a**) children and (**b**) adolescents through study.

BMI and paracetamol use in the first 12 months of life and recent use in the past 12 months (see Figure 1a; Table 1). Of these, measured height and weight data was available on 15,195 children from seven centres in seven countries and the remainder were parent-reported height and weight data. A total of 188,469 adolescents aged 13–14 years from 71 centres in 35 countries (20 affluent, 15 nonaffluent) contributed data on both BMI and recent paracetamol use in the past 12 months (see Figure 1b; Table 2). Of these, measured height and weight data was available on 44,227 subjects from 16 centres in 14 countries and the remainder were self-reported height and weight data.

The prevalence of paracetamol use in the first year of life ranged from 11% in Taiwan to 85% in Nigeria (Figure 2). There was a significant interaction between GNI and *early life* paracetamol use and subsequent childhood BMI ($P = 0.02$) in the model that controlled for age, sex, and BMI measurement type (self-reported or measured). This interaction remained when recent wheeze and maternal smoking was included in the model ($P = 0.03$). An association between *early life* paracetamol use and BMI at the age of 6–7 years was observed among affluent countries (+0.07 kg/m^2, $P = 0.002$), but not in nonaffluent countries (−0.05 kg/m^2, $P = 0.29$). These associations were similar when current wheeze and maternal

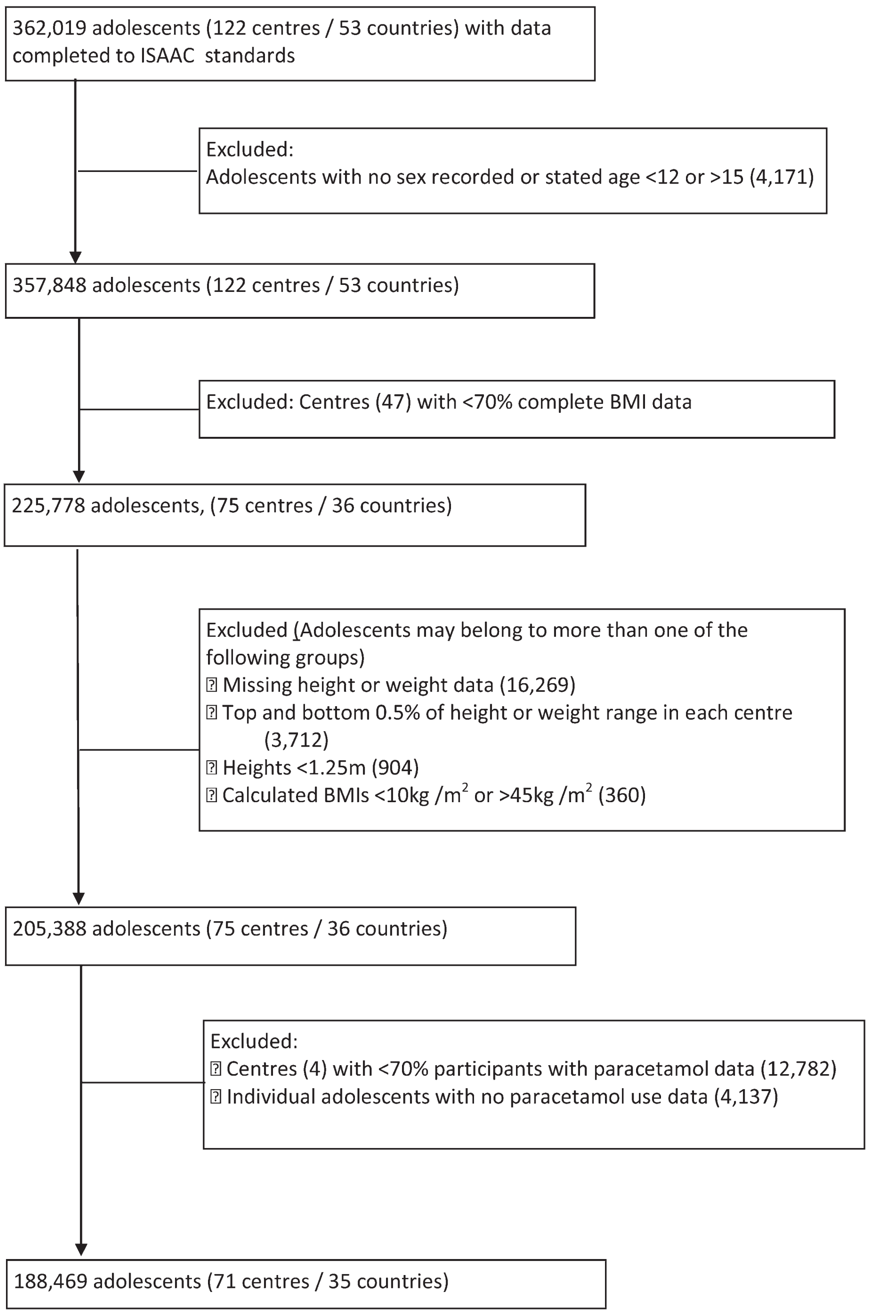

Figure 1 (Continued).

smoking was included in the model (Figure 2). When we considered only those centres with measured BMI data, there was still a significant interaction between GNI and *early life* paracetamol use and subsequent childhood BMI ($P = 0.0004$), and the effect sizes for the affluent and nonaffluent countries were $+0.23$ and -0.06 kg/m^2, respectively.

In 6- and 7-year-old children, the prevalence of high recent paracetamol use (at least once a month in the last 12 months) ranged from 2% in Japan and 67% in Nigeria (Figure 3a). There was no significant interaction between GNI, recent paracetamol use by 6- and 7-year-old children, and BMI in the model that controlled for age, sex, current wheeze, maternal smoking, and BMI measurement type (self-reported or measured) ($P = 0.57$). There was no difference in BMI among children whose parents reported that their children had high recent paracetamol use compared to those who reported low paracetamol use ($P = 0.41$) (Figure 3a). When we considered only those centres with measured BMI data, there was a significant interaction between GNI and high recent paracetamol use by 6- and 7-year-old children, and BMI ($P = 0.01$), and the effect sizes for the affluent and nonaffluent countries were $+0.26$ kg/m^2 ($P = 0.004$) and 0.00 kg/m^2 ($P = 0.99$) respectively.

TABLE 1 Characteristics of 6- and 7-year-old child participants by country

Country	(*n*)	Mean age (years)	% Female	Mean BMI (kg/m^2)	Paracetamol used in the first year of life	High[a] paracetamol use in past year
Japan	2372	7.0	49	15.5	52%	2%
Estonia	1938	7.2	49	15.9	66%	2%
Taiwan	6069	7.0	48	16.4	11%	3%
Lithuania	1990	7.5	50	15.8	66%	5%
Belgium	3728	7.3	50	15.7	82%	5%
Hungary	2386	7.4	51	16.1	56%	6%
South Korea	4921	7.4	47	16.4		7%
Poland	3876	7.5	50	15.9	66%	8%
Spain	17172	7.0	50	16.8	52%	9%
India	1718	7.0	54	13.5	66%	11%
Mexico	8750	6.9	51	16.6	50%	14%
Uruguay	1458	7.0	52	16.6	46%	15%
Portugal	969	6.8	48	16.3	81%	18%
Thailand	5831	6.8	47	16.3	79%	24%
Syrian Arab Republic	4847	6.9	52	15.6	83%	31%
Sultanate of Oman (Oman)	3748	7.2	49	14.3	79%	48%
Indonesia	2352	7.1	49	14.2	80%	48%
Nigeria	2091	6.9	50	15.0	85%	67%

[a]High paracetamol use in past year was defined as those who reported paracetamol use at least once per month.

In 13- and 14-year-old adolescents, the prevalence of high self-reported recent paracetamol use ranged from 0% in Argentina to 67% in Nigeria (Figure 3b). There was a significant interaction between GNI, recent paracetamol use by 13- and 14-year-old adolescents, and BMI in the model that controlled for age, sex, and measurement type (self-reported or measured), $P = 0.002$. An association between frequent recent paracetamol use and increased BMI at the age of 13–14 years was observed among affluent countries: frequent recent users had higher BMI values than low users (+0.17 kg/m^2, $P < 0.0001$), but not among nonaffluent countries (high users compared to low users had +0.04 kg/m^2, $P = 0.18$) (Figure 3b). These relationships remained when current wheeze was included in the model as a potential confounder. When we considered only those centres with measured BMI data, there was no significant interaction between GNI and high recent paracetamol use by 13- and 14-year-old adolescents, and BMI ($P = 0.21$), and the effect sizes for the affluent and nonaffluent countries were +0.08 kg/m^2 ($P = 0.19$) and −0.01 kg/m^2 ($P = 0.75$) respectively.

Discussion

In this large multicentre cross-sectional survey, we observed weak associations between paracetamol use and BMI among children, but only in affluent countries. We found a statistically significant association between paracetamol use in the first 12 months of life and a 0.07 kg/m^2 higher mean childhood BMI from affluent-GNI countries. Recent frequent paracetamol use was associated with a 0.17 kg/m^2 higher mean BMI among adolescents from affluent countries but there was no significant association among 6- and 7-year-old children. When only the centres with measured BMI data was used, the results were similar, with effects of higher BMI seen among those from affluent countries. However, in this smaller subset, a higher BMI was observed among children who used paracetamol (both in the first year of life, and high recent use), but not among adolescents reporting high recent paracetamol use. The highest prevalence of paracetamol use was reported in Nigeria for all three periods studied: early life (85%), and recent use among 6- and 7-year-olds (67%) and 13- and 14-year-olds (67%). The reasons for this high use are unclear, but reasons of accessibility of the drug, misunderstanding of medication indication and poverty have been previously described as contributing factors (35), although a higher prevalence of febrile and painful conditions affecting this population cannot be excluded. If paracetamol's action on indirect activation of cannabinoid receptors led to weight gain, then this effect should have been seen in all countries; however, it is possible that there were other confounders that masked the effect in poor countries.

We should be cautious in interpreting the early life paracetamol association with the small increase in childhood BMI. Firstly, this study relied on self-reported data on both height and weight as well as the assessment of paracetamol use, which was retrospective and reported after the development of the BMI outcome. However, the potential for recall bias is unlikely given that the relationship between paracetamol use and BMI is not recognized. The findings were also very similar in centres that objectively measured height and weight. Secondly, the questions about paracetamol use were imprecise, and did not enable the measurement of a gradient in the exposure intensity. Residual confounding due to factors affecting whether infants were given paracetamol in early life that are also linked to increasing subsequent childhood BMI could be a possibility. Although we were able to adjust for maternal smoking and

TABLE 2 Characteristics of 13- and 14-year-old adolescent participants by country

Country	(*n*)	Mean age (years)	% Female	Mean BMI (kg/m^2)	High[a] paracetamol use in past year
Argentina	2401	14.1	55	19.6	0%
Taiwan	8775	13.9	50	20.1	2%
China	15738	13.9	50	19.1	3%
Republic of Macedonia	2773	13.9	49	20.0	7%
Hungary	4106	13.9	51	19.5	10%
Lithuania	2504	14.0	51	18.5	11%
Estonia	3205	13.9	52	19.0	13%
Japan	1986	14.0	45	18.7	13%
South Korea	9483	14.0	44	19.5	14%
India	5010	13.9	60	18.6	16%
Finland	2803	14.0	49	20.0	19%
Cote d'Ivoire	3243	13.5	40	21.2	19%
Uruguay	4558	14.0	52	20.1	21%
Canada	2455	13.9	47	20.1	24%
Belgium	2684	14.1	51	18.8	24%
Brazil	4097	13.9	51	19.4	27%
Portugal	8413	13.9	52	20.3	29%
Peru	2592	14.0	35	19.9	29%
Poland	3887	13.9	51	18.9	30%
Spain	24002	14.1	48	20.1	31%
Ecuador	3016	13.9	51	20.9	32%
Mexico	12150	13.8	51	21.1	34%
Indonesia	7426	13.7	52	17.6	34%
Morocco	4304	13.7	50	18.6	35%
South Africa	4664	13.9	61	19.8	36%
Chile	8475	14.0	54	20.8	39%
USA	927	14.0	52	20.6	42%
Syrian Arab Republic	8529	13.6	56	19.4	43%
Bolivia	2740	13.9	52	20.5	47%
New Zealand	5831	14.2	51	21.0	48%
Sultanate of Oman (Oman)	3041	14.0	51	19.4	51%
Iran	4372	13.7	45	19.1	52%
Colombia	2407	13.9	57	19.0	57%
Fiji	3030	13.8	54	20.1	63%
Nigeria	2842	13.7	44	17.9	67%

[a]High paracetamol use in past year was defined as those who reported paracetamol use at least once per month.

recent wheeze, there may be other factors such as exposure to paternal smoking or household smoking, genetic susceptibility to both childhood febrile/painful conditions and later obesity or socioeconomic factors that both increase the receptivity to administering paracetamol in infancy and lifestyle habits that promote obesity. The interaction with GNI such that the associations between paracetamol use and BMI were only found in affluent countries suggests that reverse causality may be occurring, so that the increased BMI outcome depends on the resources and wider socioeconomic cultural background, which may differentially affect the likelihood of paracetamol use in early childhood and obesity. Alternatively, the reasons for paracetamol use could be different in affluent countries compared to less affluent countries, leading to differences in confounding by indication. Paracetamol use in low-GNI countries may be given for infective conditions such as malaria, diarrhea, and dengue fever associated with weight loss, while in high-GNI countries paracetamol may be given for conditions such as headache, which are more frequently associated with obesity.

We observed an association of recent frequent use of paracetamol with higher BMI in 13- and 14-year-old adolescents from affluent countries, but not in children aged 6–7 years. This pattern of significantly higher BMI observed among participants from affluent countries was seen in children but not adolescents when only the subset of centres with measured BMI was considered. The modest increase in BMI may be explained by the use of paracetamol to treat

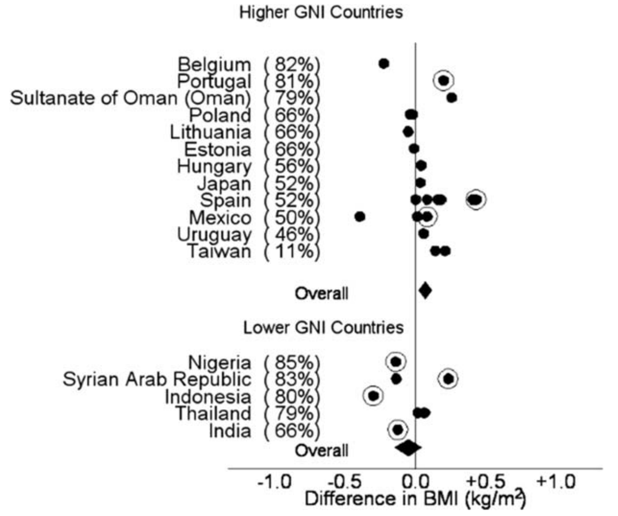

Figure 2 Associations between paracetamol use in the first year of life and differences in BMI of 6- and 7-year-old children. For each country, the proportion of children who were exposed to paracetamol is shown in parentheses. Centres with parent-reported heights and weights are shown with filled circles, and centres that measured heights and weights are shown with larger hollowed circles. The diamond labeled "overall" gives the estimate and 95% confidence limits for all the points above. GNI: gross national income refers to the total domestic and foreign output of a country and is used here as a marker of affluence.

chronic headaches, which is also known to be associated with obesity (36-38) and may be more prevalent in affluent countries (39). The rapid and varying acceleration in growth around adolescence may have reduced the power to detect an effect in the smaller subset with measured BMI data.

This study used a large number of participants providing adequate power to detect even small effects of paracetamol use on BMI among children and adolescents from many different countries. Given the interaction with GNI, our results suggest that paracetamol use may not be causally linked with increased BMI, but rather that lifestyle or other factors that correlate with paracetamol use in affluent countries may be likely to mediate this association. Further prospective cohort studies are required to investigate this association, which consider more factors associated with both obesity and fever or pain in children. **O**

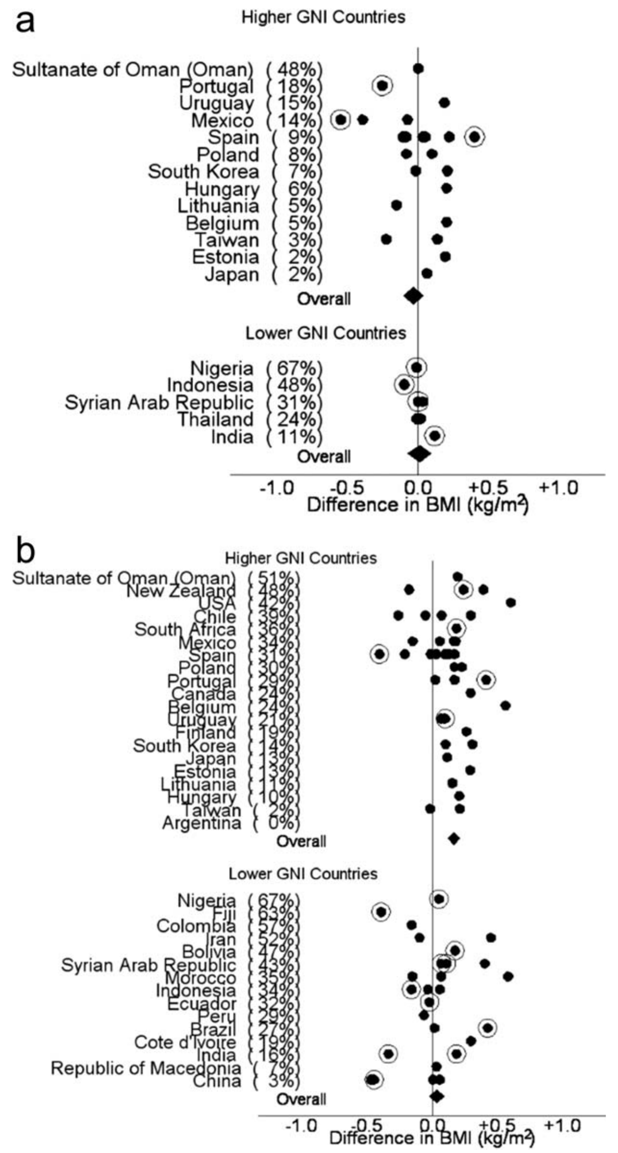

Figure 3 Associations between high recent paracetamol use, defined by paracetamol use at least once per month in the last 12 months, and differences in BMI of (**a**) 6- and 7-year-old children and (**b**) 13- and 14-year-old adolescents. For each country, the proportion of participants who were exposed to high recent paracetamol use is shown in parentheses. Centres with reported heights and weights are shown with filled circles, and centres that measured heights and weights are shown with larger hollowed circles. The diamond labeled "overall" gives the estimate and 95% confidence limits for all the points above. GNI: gross national income refers to the total domestic and foreign output of a country and is used here as a marker of affluence.

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References

1. Walsh A, Edwards H, Fraser J. Over-the-counter medication use for childhood fever: a cross-sectional study of Australian parents. *J Paediatr Child Health* 2007; 43:601–606.
2. Purssell E. Treatment of fever and over-the-counter medicines. *Arch Dis Child* 2007;92:900–901.
3. Toussaint K, Yang XC, Zielinski MA, et al. What do we (not) know about how paracetamol (acetaminophen) works? *J Clin Pharm Ther* 2010;35:617–638.
4. Anderson BJ. Paracetamol (acetaminophen): mechanisms of action. *Paediatr Anaesth* 2008;18:915–921.
5. Hogestatt ED, Jonsson BA, Ermund A, et al. Conversion of acetaminophen to the bioactive *N*-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. *J Biol Chem* 2005;280:31405–31412.
6. Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur J Pharmacol* 2006;531:280–281.
7. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* 2013;21:201–232.
8. Engeli S. Central and peripheral cannabinoid receptors as therapeutic targets in the control of food intake and body weight. *Handb Exp Pharmacol* 2012:357–381.
9. Cota D, Marsicano G, Tschop M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Investig* 2003;112:423–431.
10. Ravinet Trillou C, Delgorge C, Menet C, Arnone M, Soubrie P. CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity. *Int J Obes Relat Metab Disord: J Int Assoc Study Obes* 2004;28:640–648.
11. Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *New Engl J Med* 2005;353:2121–2134.
12. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 2005;365:1389–1397.
13. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk

factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 2006;295:761–775.

14. Topol EJ, Bousser MG, Fox KA, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet* 2010;376:517–523.
15. Gupta H, Shah D, Gupta P, Sharma KK. Role of paracetamol in treatment of childhood Fever: a double-blind randomized placebo controlled trial. *Ind Pediatr* 2007;44:903–911.
16. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA* 1995;273:929–933.
17. Howard CR, Howard FM, Weitzman ML. Acetaminophen analgesia in neonatal circumcision: the effect on pain. *Pediatrics* 1994;93:641–646.
18. Hamalainen ML, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. *Neurology* 1997;48:103–107.
19. Shepherd M, Aickin R. Paracetamol versus ibuprofen: a randomized controlled trial of outpatient analgesia efficacy for paediatric acute limb fractures. *Emerg Med Aust EMA* 2009;21:484–490.
20. Hansen EH, Holstein BE, Due P, Currie CE. International survey of self-reported medicine use among adolescents. *Ann Pharmacother* 2003;37:361–366.
21. Irwin RP. Minor analgesic use among high-school students: indications for renal morbidity and mortality. *Med J Aust* 1976;2:522–527.
22. Barea LM, Rotta NT, Stein A, Barros HM, Tannhauser M. Analgesic use for headache treatment by schoolchildren of southern Brazil. *Pharmacoepidemiol Drug Safety* 1997;6:359–366.
23. Du Y, Ellert U, Zhuang W, Knopf H. Analgesic use in a national community sample of German children and adolescents. *Eur J Pain* 2012;16:934–943.
24. Holstein BE, Holme Hansen E, Due P, Birna Almarsdottir A. Self-reported medicine use among 11- to 15-year-old girls and boys in Denmark 1988–1998. *Scandinavian J public health* 2003;31:334–341.
25. Dengler R, Roberts H. Adolescents' use of prescribed drugs and over-the-counter preparations. *J Public Health Med* 1996;18:437–442.
26. Linet MS, Stewart WF, Celentano DD, Ziegler D, Sprecher M. An epidemiologic study of headache among adolescents and young adults. *JAMA* 1989;261:2211–2216.
27. Madadi P, Enato EF, Fulga S, et al. Patterns of paediatric analgesic use in Africa: a systematic review. *Arch Dis Child* 2012;97:1086–1091.
28. Mutimer DJ, Ayres RC, Neuberger JM, et al. Serious paracetamol poisoning and the results of liver transplantation. *Gut* 1994;35:809–814.
29. Strachan DP, Cook DG. Health effects of passive smoking. 1. Parental smoking and lower respiratory illness in infancy and early childhood. *Thorax* 1997;52:905–914.
30. Chantry CJ, Howard CR, Auinger P. Full breastfeeding duration and associated decrease in respiratory tract infection in US children. *Pediatrics* 2006; 117:425–432.
31. Foliaki S, Pearce N, Bjorksten B, Mallol J, Montefort S, von Mutius E. Antibiotic use in infancy and symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old: International Study of Asthma and Allergies in Childhood Phase III. *J Allergy Clin Immunol* 2009;124:982–989.
32. Asher MI, Keil U, Anderson HR, Beasley R, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8: 483–491.
33. Ellwood P, Williams H, Ait-Khaled N, Bjorksten B, Robertson C. Translation of questions: the International Study of Asthma and Allergies in Childhood (ISAAC) experience. *Int J Tuberc Lung Dis* 2009;13:1174–1182.
34. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;64:476–483.
35. Obu HA, Chinawa JM, Ubesie AC, Eke CB, Ndu IK. Paracetamol use (and/or misuse) in children in Enugu, South-East, Nigeria. *BMC Pediatr* 2012;12:103.
36. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain* 2003;106: 81–89.
37. Bigal ME, Liberman JN, Lipton RB. Obesity and migraine: a population study. *Neurology* 2006;66:545–550.
38. Ohayon MM. Prevalence and risk factors of morning headaches in the general population. *Arch Intern Med* 2004;164:97–102.
39. Stovner L, Hagen K, Jensen R, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007; 27:193–210.