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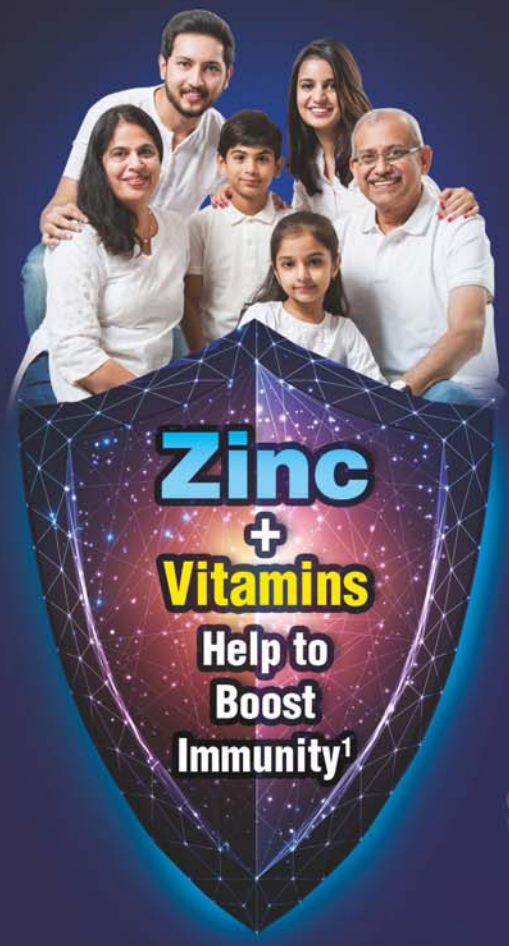

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# Indian Pediatrics

*Editor-in-Chief* Devendra Mishra

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# JOURNAL COMMITTEE AND ADVISORY BOARD FOR THE YEAR 2023

PRESIDENT'S PAGE

# Sankalp: Sampoorna Swasthya

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The advent of the 21st century brought several notable changes to our lives. Precipitated by the globalization of the 1990s, over the last two decades, our lifestyles have radically changed. Parents from my generation (myself included) are often telling children about how 'eating out' was a rarity in our childhood, our options limited, and considered an occasional luxury. We did not carry a round-the-clock connection with our friends in our pockets, and life was certainly not as sedentary as it is now. These oft-heard anecdotal lectures aside, over the past few years, I have genuinely begun worrying for the short- and long-term health effects of these changing lifestyles on our children. Studies have now shown the detrimental impact that screen time, lack of physical activity, and deteriorating climatic conditions have on the physical and mental health of children. NFHS-5 data shows that obesity amongst children in India is on the rise. There is a plethora of cheap, tasty, unhealthy options that children have quick and easy access to. Rising academic pressures, and a stressful environment inside and outside home are leading to unfortunate cases of high blood pressure, diabetes and obesity amongst school-going adolescents. Lifestyle disorders (also called non communicable diseases) have reached epidemic proportions and are increasing at alarming rates, more so in low- and middle-income countries like India. Global healthcare agencies like WHO, and the Government of India, have already identified NCDs as one of the foremost public health concerns, and have raised a call to action for the prevention of NCDs.

For the year 2023-24, the IAP will introduce a flagship program, '*Sankalp: Sampoorna Swasthya*' — a drive towards comprehensive preventive healthcare for school going children. The program is led by the belief that healthy habits, cultivated early in life, are more likely to be carried into adulthood. Childhood and adolescence are critical life stages that are primed to absorb and process new information. Hence, huge public health gains can be realized – including improvements in the health of current cohorts of children and adolescents, their future adult health trajectories, as well as the health of the next generation of children—by leveraging this crucial window of opportunity. Under the program, we are going to target five environmental and social drivers (nutrition, physical activity, screen time, substance abuse, mental health) that can have long-term repercussions on the health of the child.

There is a need to improve nutrition literacy amongst children in India by explaining what exactly balanced diet is all about. With the number of low-cost, accessible unhealthy options available in the market, it is crucial that children are themselves intrinsically driven to not give in to temptation and choose wisely between what's good and bad for their health. There is a need to regulate screen exposure and to advice young children on how to consume the content that is hurled their way every day. Observational studies note that almost all young children seem to be exposed to screen-based media by 18 months of age in the urban setting, and the average screen time is over two hours. A population-based cross-sectional study conducted in rural and urban health centers in Tamil Nadu showed that increased screen time amongst under-five children was significantly associated with developmental delay, in particular, in the domains of language acquisition and communication. The concerns about the excessive screen time among children and adolescents also pertains to a reduction in time spent on physical activity, which further exacerbates mental and physical health issues.

Reports suggest a rising threat of substance abuse amongst younger sub-populations in India (both school going and out-of-school children), with 13% of the victims of drug and substance abuse being under 20 years of age [1]. Substance abuse, or even dependency, during the formative years interferes with academic, social and life skills development of a child, and can culminate into a volatile and temperamental adulthood. Most individuals start their substance use during adolescence, but treatment is usually sought after a few years when health or other psychosocial complications begin to emerge, such that only 5% of treatment seekers are actually

adolescents [2]. The pattern suggests the importance of preventive measures to avoid later-stage dependency issues. There is also a need to address a rising number of mental health stressors amongst children in India. This is especially important as several people continue to be naysayers denying the reality and repercussions of mental health issues. We are all well aware of the harrowing reality of student suicides in India. Clearly, our children are overwhelmed with the internal and external pressures of a highly competitive academic system. Additionally, grief, fear, uncertainty, social isolation, increased screen time, and parental fatigue have negatively affected the mental health of children [3,4]. According to the Indian Journal of Psychiatry, even before the pandemic, at least 50 million children in India suffered from mental health issues. The incidence of social anxiety amongst children is further exacerbated by the flood of information through constant exposure to social media. This can drive body-image issues, and amplify eating disorders or body dysmorphia, especially amongst young girls.

As the apex organization committed to improvement of health and well-being of all children in India, Indian Academy of Pediatrics (IAP) is perfectly poised to lead a nationwide program which targets these problems. It not only has an understanding of the issues affecting children, but also has the capabilities to formulate the right approach. *Sankalp: Sampoorna Swasthya* will complement the existing education initiatives of the Government of India and State Governments, by adding expert advice and interventional capabilities at the school level. We envision the program as health education and training in schools, which should be easy to disseminate, adapt and introduce into children's lifestyle. Over the next year, IAP members will become the master trainers of the SSS program, disseminating carefully designed modules that target the five core goals of improving nutritional literacy, encouraging physical activity, regulating screen time, children's positive mental health, risk of substance abuse. Through training, capacity building, monitoring and the goal of accreditation, we will reach teachers, educators and parents via school sessions, in-person counselling and culturally and contextually rooted videos. SSS is a unique program, in that it will not restrict itself to training, but will also include follow-up support to students and parents, and strengthening of schools as effective platforms to catalyse the adoption of the Indian model of Health Promoting Schools as proposed by NCDPA to meet the best of global standards [5]. In order to achieve these objectives, SSS also intends to build strong partnerships with other stakeholders including government and NGOs and schools, to make the preventive services robust, sustainable, standards-driven, and effective. In the past 60 years of its existence, IAP has done tremendous work for the benefit of the children and adolescents of India, by continuously upgrading the knowledge and skills of pediatricians, advising governments on critical issues and advocacy on several fronts. Now, in its Diamond Jubilee year, it is only apt that through SSS, IAP is poised to take a big leap forward, by taking the benefits of the best of science, directly to the community and doorstep of all school going children of India, in an unprecedented manner.

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INVITED COMMENTARY

# High Birth Weight and Risk of Childhood Obesity

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Childhood obesity has emerged as an important global public health problem [1]. India has also experienced an increase in prevalence of childhood overweight and obesity in the last three decades [2]. Childhood obesity is associated with various metabolic disorders such as type 2 diabetes, dyslipidemia, hypertension, and fatty liver disease [3]. Additionally, cardiovascular events and mortality during adulthood are associated with obesity during childhood [4]. Therefore it is imperative to identify modifiable factors during early life that play in role in development of obesity in children [5].

Nutritional and environmental influences in the intrauterine period affect weight gain and cardiometabolic risk factors in the offspring during childhood and adult life [6]. Epigenetic mechanisms that alter gene expression without changing the DNA sequence in addition to genetic and environmental factors form the basis for the "metabolic programming." Higher maternal prepregnancy weight, excessive weight gain during pregnancy and gestational diabetes mellitus are associated with weight gain in children and adolescence. In addition, family history of obesity increases the predisposition for excess weight gain. These factors account for intergenerational transmission of obesity and metabolic disorders. Nutrition during infancy and early childhood also influences weight gain during later childhood. Breast feeding has a protective effect against childhood obesity. In contrast, rapid weight gain during infancy and early adiposity rebound are associated with higher risk for subsequent development of obesity.

The increase in prevalence of childhood overweight and obesity in India has been noted not just in the higher socioeconomic groups but also in the lower income groups [2]. In a study published in this issue of the journal, Kumar, et al. [7] conducted a retrospective birth cohort study among children 7 to 10 years of age in 22 villages in the state of Himachal Pradesh. Birth weight data was obtained from immunization cards of children born in year 2011-2012. Specific questionnaires were administered to obtain information on gender, years of schooling, diet and physical activity. The relative risk of elevated body mass index (≥2 SD) between age 7-10 years was 5-fold higher in children with a birthweight of more than 3500 grams in comparison to those with a birth weight of between 2500 and 2999 g, after adjustment for several confounding variables such as mean age, gender, mean years of schooling, dietary habits and physical activity. A major strength of the study by Kumar, et al. [7] is that it is community based and not hospital or clinic based, as has been the case in previous longitudinal birth cohorts in India. The rural setting in northern India is another strength as overweight/obesity are more prevalent than under nutrition in rural India [8]. Moreover, in a study that pooled data from 52 studies conducted in 16 of the 28 states in India, the combined prevalence of childhood and adolescent obesity was higher in northern India than in southern India [2]. Limitations of this study include the small sample size (379 children with birth weight between 2500 and 2999 g and 377 children with birth weight of more than 3500 g) and lack of information on growth parameters during early infancy such as catch-up growth and timing of adiposity rebound. Additionally, the investigators did not adjust for maternal characteristics that can affect obesity in offspring such as age, prepregnancy body mass index, glycemic status, and weight gain during pregnancy.

The findings of a positive association between birth weight and childhood overweight/obesity in children from rural northern India are similar to those from previous studies in other countries. In a 12-country study that included high income, middle income and low-income countries, birth weight ≥3500 g was associated with a higher prevalence of obesity in children 9-11 years of age [9]. Most importantly, these associations have been stable during the development of the obesity epidemic as demonstrated by increased risk for overweight between age 6 to 13 years in a population based Danish cohort study of children born between 1936 and 1983 [10]. The increased risk for childhood overweight with higher birth weight is evident as early as 3 years of age as was shown in a Chinese birth cohort study [11]. The long-term

consequences of high birth weight on obesity extend beyond childhood into adult life [12,13].

The findings by Kumar, et al. [7] suggest an association but do not imply a cause effect relationship. Further longitudinal studies are warranted to determine if targeting modifiable prenatal risk factors such as optimizing maternal nutrition, pre-pregnancy body mass index, gestational weight gain and glycemic status will result in reduced risk of overweight and obesity in the offspring [5]. Given the crucial role played by environmental factors in addition to genetic and epigenetic factors, it would be important to utilize a multipronged approach including healthy nutrition and active lifestyle during infancy and early childhood to effectively prevent the development of childhood obesity.

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INVITED COMMENTARY

# Birthweight: An Early Beacon of Children's Growth!

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What are the origins of obesity? How are the causes related to genetic predispositions and to environmental and behavioral exposures, such as overeating and insufficient physical activity? With obesity being one of the most impactful diseases experienced by contemporary cohorts in many places around the world, including India, the answer to this question has major implications for policies, programs, and recommendations aimed at improving individual and population health. Though some researchers have proposed that obesity has common-sense solutions rooted in maintaining energy balance, it is increasingly clear that obesity is a complex condition that develops and becomes entrenched over time. We are becoming increasingly aware that at least some of the risk of obesity is set early in life.

This early life risk may have origins even prior to birth, involving prenatal exposures and growth patterns [1]. Prenatal exposures are measured in terms of birthweight or birthweight for gestational age. Clinically, birthweight of under 1500 g is considered critically low; 1500-2500 g is considered low, and over 2500 g is considered normal [2]. Recent studies have also started to raise concerns about high birthweight, identifying high risks of later developing some conditions for people with birthweight higher than 3500 g. Birthweight is best considered in the context of gestational age, as a child born prematurely with low birthweight has different health risks compared with a child born at term of the same size, whose low birthweight may be an indicator of intrauterine growth retardation.

The relationship between birthweight and body size, including obesity, in childhood, and even in adulthood, has been an area of extensive research across populations. Early studies, for example from the Nurses' Health Study in the US, reported a U-shape relationship between birthweight and body size in adulthood, with high prevalence of obesity among people who had both low and high birthweight [3]. Some recent studies have reported a J-shaped relationship, with the risks for obesity being elevated for both low and high birthweight, but more so for the latter [4]. Research on contemporary child cohorts have reported linear associations between birthweight and childhood weight, with weight status and abdominal adiposity in childhood and adolescence increasing steadily for children according to their weight at birth, especially for girls [5]. A systematic review reported that, across studies, children and adolescents who were small at birth are more likely than those who were large at birth to experience rapid growth during early childhood. However, children who were bigger at birth and who also grew quickly had the highest odds of developing overweight or obesity [6]. The same issue has also been addressed in a rural cohort in India by Kumar, et al. [7] in their study published in this issue of the journal.

To be able to understand these predispositions and apply the findings to obesity prevention, we must first understand the underlying mechanisms. Some components of the observed predisposition to obesity are likely genetic [8]. The likelihood of being obese is higher among children with obese parents [9]. Still, the roles of genetic predispositions, environmental exposures, and behavioral patterns in intra-family similarities are difficult to disentangle. Twin studies have attempted to separate out heritability from shared exposures and behaviors, and have reported high heritability of BMI (body mass index) ranging from 41% to 85%, with the association increasing with age [10].

In addition to genetic predisposition, contextual factors are also important, and can begin even prenatally. Indeed, genetic factors and environmental factors may interact, leading to different risks, even for children growing up in the same environments. Mother's health, for example, suffering from obesity or diabetes, her nutritional intake during pregnancy, and her exposure to stress, have been shown to affect intrauterine growth and weight status [11]. Mother's health-related behaviors during pregnancy are shaped by contextual factors and are also relevant to birthweight, for example smoking and drug intake, eating behaviors, and activity levels [12]. Contextual factors and maternal and family behaviors

affecting growth in utero tend to continue after a child's birth. For example, children whose mothers had insufficient food during pregnancy are likely to experience insufficient food in childhood, shaping their postnatal growth.

Birthweight is an important measure of wellbeing at birth and is an early signal of subsequent health trajectories. In exploring the explanatory power of birthweight, it is important to not overlook its complexity, nor the complexity of weight status subsequently in life. Growth is linear, and it is important to consider it as such in analyses. A child with birthweight of 3501g is more similar in weight to a child whose birthweight is 3499 g than to one whose birthweight is 4,000 g. Treating birthweight as a categorical variable ignores this and creates false cut-points. Not considering the entire birthweight spectrum, for example leaving out of analyses children who are in specific ranges of birthweight, further contributes to inadequate analysis of birthweight and its implications for subsequent health.

Another strategy for analyzing birthweight in a correct and actionable way is to avoid treating it as an exposure – children are not exposed to birthweight the way they are exposed, for example, to air pollution. Rather, their exposure to air pollution affects both their birthweight and their subsequent growth and their risks of unhealthy weight in childhood and adulthood. Birthweight is an early measure of an individual's growth and provides an opportunity for clinicians and programs to identify children whose growth trajectories have started off at a suboptimal level due to pre-dispositions and exposures. The more we can understand how early exposures track during childhood, including by using birthweight as a beacon, the more opportunities we can create to prevent unhealthy weight, both overweight and underweight, both of which are major contributors to poor health in India.

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PERSPECTIVE

# Congenital Heart Disease: Would It Be the Key Driver of Infant Survival During *Amrit Kaal* (2022-2047)?

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Post-independence, we made significant strides in childhood survival. However, there is an abysmal improvement in survival due to birth defects. Globally, India contributes the largest proportion of under-5 deaths, overall as well as due to birth defects. Congenital heart disease (CHD) is the single most common cause of birth-defect related deaths, and is the 7th most common cause of infant deaths. Scarcity of pediatric cardiac care professionals and pediatric cardiac centers has led to a huge demand-supply gap. Understanding the burden of CHD and taking imperative steps at primary, secondary and tertiary levels are essential during *Amrit Kaal* (2022-2047). Coverage of management of CHD under *Janani Shishu Suraksha Karyakram, Rashtriya Bal Suraksha Karyakram* and *Ayushman Bharat* programs offers a huge promise, as shown by the experience from *Hridayam* program in Kerala.

**Keywords:** *Birth defects, Infant mortality, Neonatal mortality, Under-5 deaths,*

Despite significant reduction in child mortality, India, a country with low-middle socio-demographic index (SDI), contributes the largest proportion of under-5 deaths to the world statistics [1]. During 1990-2017, contribution of birth defects to child mortality has increased, with reducing neonatal mortality rate (NMR) and under-five mortality rate (U5MR) [1,2]. We also contribute maximum to the global under-5 deaths attributable to birth defects [2]. Congenital heart diseases (CHD) contribute the most to birth defects (28%), and the single most common cause of deaths due to them [3,4]. Here, we discuss the significance if CHDs with respect to child mortality, our preparedness, and the way forward to deal with the situation during the 'Amrit Kaal' of our independence (2022-2047).

## CONGENITAL HEART DISEASE AND CHILD MORTALITY

During the last three decades, child survival improved significantly due to improvement in antenatal and neonatal care, control of vaccine-preventable diseases, acute respiratory tract infections and diarrhea-dehydration, and nutritional programs. During 1990-2019, the NMR, infant mortality rate (IMR) and U5MR reduced significantly The data from the Sample Registration System (SRS) revealed birth defects moving up from the eighth to the fifth most common cause of infant deaths during the 12-years period (2004-06 vs 2015-17) [5,6].

General improvement in childhood survival during 1990-2017 increased the proportional contribution of birth-defects to U5MR [2]. Concurrently, improving diagnostics and increasing awareness led to a steady rise in the reported prevalence of CHD [7,8]. The two together moved CHD up from 8th to 7th most common cause of infant mortality [9]. With birth prevalence of CHD being 0.9% (range, 0.8-1.2%), estimated annual birth prevalence (EABP) in India is likely to be upwards of 2,40,000 [8]. EABP of CHD in different regions are as follows– 84,000 in Northern region (Jammu-Kashmir, Laddhakh, Punjab, Himachal Pradesh, Uttarakhand, Punjab, Haryana, Chandigarh), 52,000 in Eastern region (Bihar, Jharkhand, Odisha, West Bengal), 38,000 in Southern region (Telangana, Andhra Pradesh, Tamil Nadu, Karnataka, Kerala), 29,000 in Western region (Maharashtra, Gujrat), 23,000 in Central region (Madhya Pradesh, Uttar Pradesh, Chhatisgarh, Rajasthan) and 12,500 in North-eastern region (Assam, Sikkim, Meghalaya, Mizoram, Nagaland, Manipur, Arunachal Pradesh, Tripura) [8]. About 25% of these babies have critical CHD (i.e., requiring interventions in the first year of life). Many of these babies mimic sepsis and/or respiratory diseases during neonatal period, or get complicated with one.

For the lack of timely surgery, children with CHD consume healthcare resources unproductively for repeated hospitalizations for congestive heart failure, recurrent pneumonia, cardiovascular complications,

malnutrition and its associated problems. With passage of time, surgical outcome would be compromised in many, while many children would become inoperable. Thus, CHD is also an important cause of mortality and morbidity during later childhood as well. In fact, birth defects (of which CHD constitute the largest proportion) are estimated to contribute 8% of under-5 deaths in India [1]. Contribution is likely to be more in states with U5MR<25, e.g., Kerala, Tamil Nadu, Maharashtra, Delhi, Manipur and Nagaland. The same is likely to happen in most of other states as they are projected to achieve U5MR<25 by the year 2030, barring Uttar Pradesh, Madhya Pradesh, Chhatisgarh, Odisha, Rajasthan, Assam and Mizoram [1]. Another analysis revealed birth-defects to be the third leading cause of early neonatal mortality in 17 states [2]. With persistently improving SDI, awareness, institutional deliveries, neonatal, infant and under-5 survival, and lack of healthcare infrastructure to manage CHD in majority of states, a fairly constant birth prevalence of CHD would create a case of 'perceptual explosion' during the *Amrit Kaal*.

## CURRENT STATUS

### Care of Children With CHD

Level of care available for children with CHD varies significantly between high income countries (HICs) and low- and middle- income countries (LMICs). In HICs, the vast majority reach adulthood owing to breakthroughs in diagnosis and management. This; however, is not the case in LMICs. One fully equipped cardiac centre is estimated to serve a population of 1,20,000 in North America, while the same serves a population of 16 million in Asia. Similarly, one cardiac surgeon serves a population of 3.5 million in North America and Europe, while the figure in Asia is 1 per 25 million [8]. In India, a population of 141 crore is served by a handful of centers. We have very few trained professionals in various disciplines of pediatric cardiac sciences and intensive care. Scarcity of facilities in public sector hospitals is even more glaring. Even within the country, available pediatric cardiac facilities are unevenly distributed [8].

Until recently, children with CHD were being managed through out-of-pocket expenditure. Thus, the majority were unable to afford timely surgery. Implementation of flagship public healthcare schemes [e.g., Pradhan Mantri Jan Arogya Yojana (PM-JAY), Janani Shishu Suraksha Karyakaram (JSSK) and Rashtriya Bal Swasthya Karyakram (RBSK)] is likely to become a game-changer. Despite availability of funds through such schemes, proportion of children with CHDs getting operated differs substantially across different regions of the country — Central region (7.6%), Eastern region (12%), Northern region (17%), Western region (28%), Southern region (74%), while none get operated in the North-Eastern region [8,10]. Capacity, both infrastructure and human resource, is the prime limitation for the observed demand-supply gap, especially in northern and eastern regions.

### The Hridyam Program

IMR in Kerala was 16/1000 livebirths in 1991, and it stagnated around 10-12 for about a decade (2007-2017), despite reduction in neonatal and infant deaths with improvement in perinatal care, infectious diseases and malnutrition— the so-called 'low-lying fruits.' Birth-defects (of which CHD has the largest share) were found to be major contributor to infant death, and the second most common cause of under-5 deaths [2,11]. A plan of 'paediatric cardiac care continuum' was worked out to address the issue of CHD, especially the critical ones. It was implemented in August 2017 as '*Hridyam'* program in public-private partnership. Children (aged 0-18 years) with suspected CHD were registered to develop a life-time pathway instead of just providing one-time surgery. Program created a state-wide network connecting primary health centres to tertiary hospitals for timely and optimal management [11]. It led to fall in all-cause IMR to 6/1000 livebirths by the year 2019 (**Fig. 1).** Jammu-Kashmir, Punjab, Himachal Pradesh, Delhi, West Bengal, Maharashtra, Goa, Tamil Nadu and all Union Territories have already achieved an IMR of 20 or lesser, and more states are expected to join the league soon [1,12]. The CHD program may perceived to be expensive, cumbersome and unyielding, experience and evidence from the '*Hridayam'* program; however, suggest this to be the only way to reduce IMR further in these states.

## THE WAY FORWARD

The Government of India is committed to achieve 'single digit' NMR by 2030 and U5MR of 23 by 2025 [13,14]. Stagnating contribution of neonatal deaths to under-5 deaths (i.e., ~55%) across states irrespective of their U5MR and SDI [1] suggests the need to shift on to the next paradigm of interventions. Birth-defect surveillance and management program is likely to reduce U5MR further, especially in states with U5MR<25 [2]. Diagnosis and management of CHD would be the most important aspect of this program.

### Continuum of Care Through *Ayushman Bharat*

Experience from countries with high SDI revealed that identification of newborns with CHD before discharge from hospital, excellence in emergency care, and developments in pre-operative and post-operative intensive care, cardiopulmonary bypass and surgical techniques have dramatically improved survival of children with CHD [15].

*Hridayam* program provided a made-in-India model of community-based pediatric cardiac care continuum (beginning from the antenatal period to the postnatal evaluation, cardiac surgery and long term follow up), which may be replicated in other parts of the country. The experience gained may inform a national policy for children with CHD, which may work to develop a similar approach integrating JSSK and RBSK with PM-JAY. As part of comprehensive primary health care, obstetricians and sonographers at Health and Well-being Centers (HWCs) and district hospitals may be trained to detect CHD during antenatal period. Inclusion of essential physical cardiac examination and pre-discharge screening by pulse oximetry in the existing neonatal protocols would help to detect CHD before discharge. Healthcare providers may be trained to identify survivors of neglected CHD presenting to healthcare facilities or detected through school health programs. Suspicion of CHD would prompt timely referral and transport of in utero baby, neonate or older child to a designated tertiary care centre for detail assessment. Children with CHD thus identified may receive secondary and tertiary healthcare under public-funded schemes. Integration of HWCs with secondary and tertiary care centers may be enabled through care pathway linkages and information technology by creation of Ayushman Bharat Health Account (ABHA) ID, which would create a longitudinal health record for babies with CHD. Recently, follow up packages has been added under PM-JAY to provide continuous support even after discharge from hospital. National Health Authority introduced a digital payment voucher, e-RUPI to ensure uninterrupted access to diagnostics and therapeutics from providers of patients' choice. These person- and purpose-specific payment vouchers means public subsidy is provided only to the needy and only for the intended purpose. Early diagnosis, prompt referral, provision of affordable treatment, combined with better post-operative home-based care, would be a game-changer in bringing down the attributable infant and child mortality.

## Developing Pediatric Cardiac Care Services in the Public Sector

Establishing at least one premier Center of Excellence (CoE) in each region is an urgent need of the hour. Northern and eastern regions may be prioritised in view of wider demand-supply gap; the former has lower U5MR as well. These centers should have five essential, distinct and child-specific specialized clinical service verticals working in horizontal collaboration– Pediatric (diagnostic and interventional) Cardiology, Pediatric Cardiac Radio-imaging, Pediatric Cardiac Intensive Care (to provide specialized intensive care services before and after cardiological intervention and cardiac surgery), Pediatric Cardiac Surgery and Pediatric Cardiac Anaesthesia. Cardio-pulmonary bypass, extracorporeal membrane oxygenation and pediatric cardiac critical care nursing services are essential component of the CHD program. Ancillary services should include Pediatric Cardiac Airway, Pediatric Cardiac Pulmonology and Cardiac Genetic services. Creating CoEs in the established institutes of national importance (INIs), as extension of their pediatric services, is likely to be logistically and financially prudent. These CoEs would act as apex institutions, and would provide training-learning opportunities, develop academic

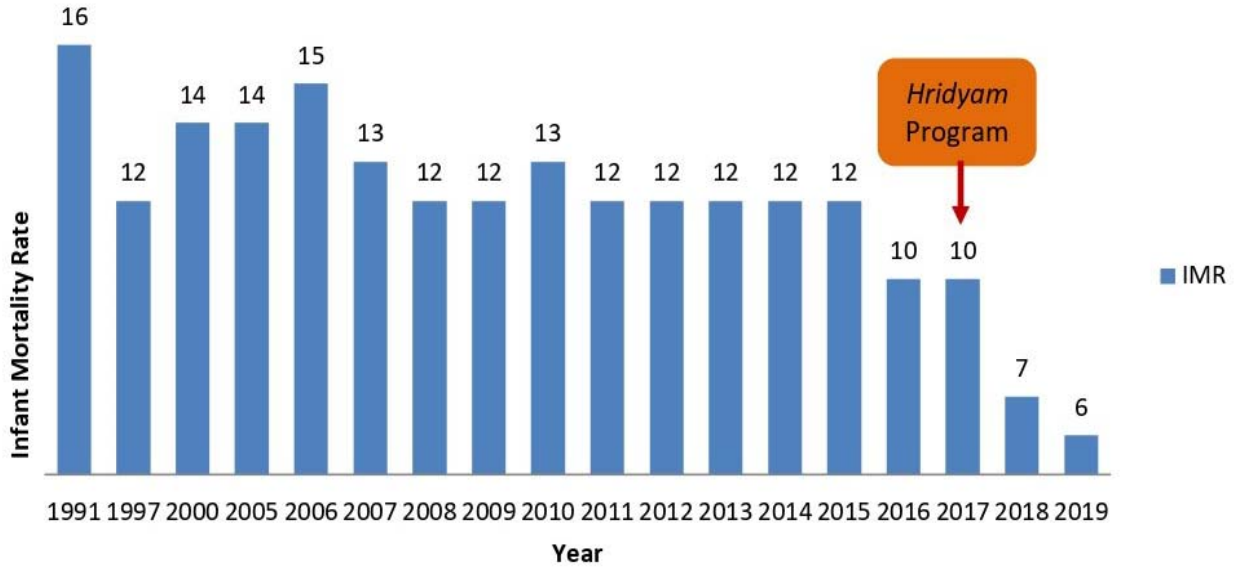


**Fig. 1** Effect of Hridayam program on the stagnating infant mortality rate in Kerala (1991-2019).

programs, help capacity-building and stimulate country-specific research and innovations [8].

*Strengthening behaviour change communication:* Public awareness needs to be created about long-term survival of most of the CHD patients. It may improve health-seeking behavior within community. Emphasis on primary prevention by reducing consanguinity, immunization against rubella, reducing risk factors like smoking, alcohol intake during pregnancy, supplementing folic acid during first trimester, and optimal control of diabetes should also be on cards [16].

### Human Resource Development

Management of CHD needs development of specialized professionals in various disciplines of pediatric cardiac sciences as mentioned above. At present, we only have a post-doctoral (DM) program in Pediatric (diagnostic and interventional) Cardiology, and that too only at All India Institute of Medical Sciences-Delhi and Postgraduate Institute of Medical Education & Research-Chandigarh. There are no post-doctoral programs in the other four essential disciplines. While establishing CoEs may be a long-term goal, post-doctoral programs need to be started immediately with horizontal integration of resources from Departments of Pediatrics, Cardiology, Cardiovascular Surgery, Radiodiagnosis and Anesthesia in the established INIs **(Table I)**. The National Medical Commission (NMC) and National Board for Examinations in Medical Sciences (NBEMS) may find inclusion of these academic programs in their bouquet of post-doctoral courses as visionary, and as need of country's near future. Training programs to create a pool of perfusionists, pediatric cardiac critical care nurses and other professionals required for in-hospital and out-of-hospital care of children with CHD may also be planned (**Table I)**. Initiation of pediatric cardiac services and training programs in various disciplines of pediatric cardiac sciences in the new generation of tertiary healthcare institutions of national importance (e.g., the new All India Institutes of Medical Sciences) and the autonomous tertiary healthcare institutions under various state governments would significantly improve the access across the country. They would also help create locally-relevant innovative approaches towards CHD program. These initiatives are likely to lead to development of a comprehensive and sustainable India-made ecosystem to effectively deal with the epidemiological transition during *Amrit Kaal* (2022-2047).

### Deliverables

Improved childhood survival is likely to improve life expectancy at birth and thus our Human Development Index [1]. Creation of a large public-funded healthcare scheme would lead to new investments in healthcare, pharmaceutical, manufacturing and biomedical engineering sectors. A relatively stable birth prevalence of CHD, large population, huge demand-supply gap and locally relevant research/innovation would make the indigenously developed CHD program self-sustainable, scalable and replicable. Shift of care of CHD from currently dominant private corporate hospitals to the public healthcare delivery system is likely to benefit domestic industry, as has been seen in the vaccine sector [17,18]. An economically competitive CHD program could also foster medical tourism. All these would end up generating employment for unskilled, skilled and highly skilled personnel. In a nutshell, such a CHD program would fulfil objectives of Atmanirbhar Bharat Abhiyaan, Heal-in-India and Health-by-India programs, and would be an important component of roadmap to India@100.

## CONCLUSIONS

With reducing child mortality, CHD is becoming a key driver of childhood survival. Multilateral collaboration between

**Table I Proposed Training Programs in Various Disciplines of Pediatric Cardiac Sciences**

| *Courses* | *Disciplines* | *Eligibility* |
|---|---|---|
| DM | Pediatric Cardiology (Diagnostic and Interventional services) | MD/DNB (Pediatrics) |
| DM | Pediatric Cardiac Intensive Care (Intensive Care services before and after cardiological interventions and cardiac surgeries) | MD/DNB (Pediatrics/Anesthesia) |
| MCh | Pediatric Cardiac Surgery | MS/DNB (Surgery) |
| DM | Pediatric Cardiac Anesthesia | MD/DNB (Anesthesia) |
| DM | Pediatric Cardiac Radio-imaging | MD/DNB (Radiology/Radio-imaging) |
| B. Sc. | Perfusion Tecnology | I.Sc. (Biology) |
| Postgraduate fellowship | Pediatric Cardiac Nursing | M. Sc. (Pediatric Nursing) |
| Postgraduate fellowship | Pediatric Cardiac Critical Care Nursing | M. Sc. (Pediatric Nursing) |
| Postgraduate fellowship | Pediatric ECMO Nursing | M. Sc. (Pediatric Nursing) |

policy makers, administrators, public health delivery system, private hospitals and pediatric cardiac professionals is urgently needed. It would help in developing and implementing pediatric cardiac care continuum across the country. At least one CoE per region needs to be established, prioritizing the under-served regions. Professional training programs may be initiated to create a sustainable ecosystem. An evidence-informed national policy may go a long way in managing the imminent epidemic of CHD, improving HDI ranking, and generating jobs in the run up to the centennial celebrations of our independence in the year 2047.

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RESEARCH PAPER

# Risk of Childhood Obesity in Children With High Birth Weight in a Rural Cohort of Northern India

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**Objective:** To compare the risk of early childhood obesity (BMI *z*-score of ≥+2SD) among children of more than 7 years of age with a birth weight of more than 3500 g to a birth weight of 2500-2999 g.

**Methods**: Retrospective birth cohort study among children of 7 to 10 years of age in 22 villages of Himachal Pradesh with not-exposed (birth weight: 2500 to 2999 g) and exposed (> 3500 g) group.

**Results:** A total of 379 and 377 participants were enrolled in not-exposed and exposed group, respectively. Adjusted relative risk (aRR) between exposed and high BMI (>+2SD) was 4.9 (95%CI: 1.3-17.5) adjusted for mean age, gender, mean years of schooling, consumption of butter, fruits, vegetables, and indoor playing.

**Conclusion:** High birth weight (>3500 g) increases and normal birth weight decreases the risk of childhood obesity up to five times in rural India.

**Keywords**: *Body mass index, Catch-up growth, Outcome, Overweight.*

The nutrition in utero influences the risk of developing chronic diseases in adulthood like obesity, metabolic syndrome, and heart diseases [1]. Maternal nutrition and health status affect in utero growth and development reflected by birth weight as an outcome [2]. High birth weight (>3500 g) is associated with morbidities later in life like obesity and associated chronic diseases [3,4]. Adiposity during childhood and adolescence was related to a high level of blood glucose, insulin, and insulin resistance [5]. Apart from in utero nutrition and health, postnatal dietary patterns are also associated with chronic diseases in adulthood.

India observed a rising trend of overweight and obesity in both high and low socioeconomic groups [6]. Childhood overweight and obesity warrants early detection and appropriate intervention for the prevention of chronic diseases. Longitudinal studies and birth cohorts provide evidence for causal relationship between risk factors and chronic diseases in adulthood during antenatal and postnatal period. Indian birth cohorts have been established and followed up to delineate risk factors associated with chronic diseases [7,8]. Similar data of birth cohort in rural areas of northern India are limited [9]. Likewise, other studies from India were hospital-based [10,11], or were done in southern part of India around immediate vicinity of a metropolitan city [12,13]. Cultural and dietary diversity has been observed in rural India for preference of food items, ways of cooking food, and pattern of physical activity.

This study was done to measure the relative risk for early childhood obesity among children more than 7 years of age with a birth weight of more than 3500 g as compared to birth weight of 2500-2999 g in rural northern India.

## METHODS

A retrospective cohort study was conducted in 22 villages of a health block of district Una, Himachal Pradesh, covering a population of about 6.9 million with 1.4 million households. The local census by the health administration showed that the health block had a population of 71,416 with 14,107 households. The study was approved by the institutional ethics committee.

*Invited Commentaries: Pages 94-97*

Children with birth weights from 2500 to 2999 g were considered as not-exposed and more than 3500 g as an exposed group. The category of birth weight 3000-3499 g was not included to avoid overlap between high (exposed) and normal (not-exposed) birth weight. Inclusion criteria for recruitment were children who possessed immunization

cards mentioning her/his birth weight, born in year 2011-12, a native resident of the village, and with an informed consent of parents. Participants with a known cause for pathological obesity were excluded from the study. Recruitment was carried out in two phases: phase-I (2013-14) and phase-II (2021-22).

Data were collected by a trained field attendant using a pretested questionnaire containing information about background characteristics like gender, socioeconomic status, and schooling, followed by diet and physical activity. Dietary assessment was done using interviewer-administered questionnaire where information regarding consumption of food items like fruits, vegetables, cooking oil, additional butter/ghee while eating, salt while cooking were collected from parents of participants. For the study purpose, indoor physical activities were focused on activities requiring mild exertion like carrom board, ludo, mobile games, playing with toys without physical exertion, etc. whereas, outdoor activities included moderate to severe exertion like cricket, football, race, etc. Udai Pareek scale was used to measure socioeconomic status in both phases of surveys. Anthropometric assessment was done for body height (in meters) without shoes by Seca portable stadiometer (Seca Corporation) with participant's head in the Frankfurt plane, and body weight (in kg) was measured by a portable Tanita SC-240 body composition analyzer (Tanita Corporation) with minimal light clothing and removal of heavy clothing, pocket items, and shoes. Both height and weight were measured twice, and a third time only if the difference in the two values of height and weight was more than 0.5 cm and 0.5 kg, respectively. The final value was an average of the two closest values. Body fat (in percentage) was measured by Tanita SC-240 body composition analyzer and two consecutive measurements were taken. If the difference between the two measurements was more than 2.0%, a third value was taken and an average of two closest values was considered for analysis. Body mass index (BMI) was calculated for every child by dividing weight (in kilograms) by the square of height (in meters). The BMI *z*-score was calculated using age- and sex-specific reference data as per the World Health Organization (WHO) charts. Obesity was defined as BMI *z*-score more than 2 standard deviations (SD).

Sample size assumptions were made with incidence of obesity of 11% in not-exposed and 15% in the exposed group with a relative risk (RR) of 1.7 [18]. The sample size of 748 (374 in each group) was calculated at 5% level of significance and 80% study power.

*Statistical analysis*: Data were entered in Microsoft Excel and analyzed using the R studio software package (version 3.3.1). Unpaired students *t* test and chi-square test were used to compare for statistical significance for continuous and categorical variables between groups. The relative risk (RR) with a 95% confidence interval (95% CI) was calculated to assess the strength of association between birth weight and childhood obesity. Binary logistic regression analysis was done to observe unadjusted RR and adjusted RR (aRR) of obesity and high birth weight for child age, gender, years of schooling, mean fraction of time spent playing indoors, and consumption of fruits, vegetables, and Ghee/butter. Variables that were significantly different in descriptive analysis. The analysis was also adjusted for potential confounders like the age of the mother and socioeconomic status.

## RESULTS

A total of 399 (93 exposed, 306 non-exposed) participants were enrolled in the first phase and 349 (284 exposed, 73 non-exposed) in the second phase. The mothers were the respondent for all participants.

The sociodemographic characteristics and dietary consumption patterns are shown in **Table I**. None of the families in both groups were consuming salt more than 5 grams of salt per person per day. Fried food consumption was observed to be high but the difference was statistically indifferent (**Table I**). The physical activity assessment and anthropometry compared between non-exposed and exposed groups are shown in **Table II**.

The risk ratio (RR) (95% CI) of high BMI ( ≥+2SD) high birth weight (>3500 g) was 7.0 (2.1-13.8; *P*=0.002), which was statistically significant even when adjusted for age, gender, years of schooling, consumption of butter, daily consumption of fruits and vegetables, and proportion of time played indoor [aRR (95%CI) 4.9 (1.3-17.5); *P*=0.005]. With high BMI, adjusted measures of association was significant only for females [aRR (95%CI) 0.4 (0.1-0.9); *P*=0.037]. Adjusted association was statistically significant between low BMI ( ≤-2SD) and exposed group [aRR (95%CI) 0.5 (0.4-0.7); *P*<0.001].

## DISCUSSION

The current rural birth cohort study observed a significant association of high birth weight (more than 3500 g) than normal birth weight (2500-2999 g) with obesity. The outdoor physical activity assessment was similar in exposed and non-exposed group.

The current study was a birth cohort with an adequate sample size in a rural setting. The non-inclusion of birth weight category of 3000 to 3499 g in the sample avoided the exposure ascertainment bias. Potential covariates like mean fraction of time spent on indoor physical activity, addition of extra *ghee*/butter, and frequency of healthy diet

**Table I General Characteristics of Rural Cohort of Himachal Pradesh**

| *Characteristics* | *Not exposed (n=379)* | *Exposed (n=377)* | *P value* |
|---|---|---|---|
| Respondent age (y)[a] | 33.5 (4.2) | 33.9 (4.2) | 0.133 |
| Birth weight (kg)[a] | 2.6 (0.4) | 3.7 (0.2) | <0.001 |
| Age of child (y)[a] | 8.6 (1.1) | 9.0 (1.0) | <0.001 |
| Child age-group | | | |
| 7 | 68 (17.9) | 33 (8.8) | <0.001 |
| 8 | 120 (31.7) | 89 (23.6) | 0.012 |
| 9 | 94 (24.8) | 99 (26.3) | 0.631 |
| 10 | 97 (25.6) | 156 (41.4) | <0.001 |
| Female | 194 (51.2) | 159 (42.2) | 0.012 |
| SES categories | | | |
| Lower middle | 28 (7.4) | 16 (4.2) | 0.060 |
| Middle | 283 (74.7) | 283 (75.1) | 0.899 |
| Upper middle | 68 (17.9) | 78 (20.7) | 0.329 |
| School going | 377 (99.5) | 377 (100.0) | 0.169 |
| Public school | 293 (77.7) | 276 (73.2) | 0.150 |
| Duration of education (*y*)[a] | 2.7 (1.3) | 3.2 (1.2) | <0.001 |
| Breast fed | 365 (96.3) | 361 (95.8) | 0.724 |
| *Ghutti*/honey | 364 (96.0) | 361 (95.8) | 0.889 |
| Vegetarian | 296 (78.1) | 303 (80.4) | 0.435 |
| Days in a week of fruits consumption | 6.3 (1.4) | 6.4 (1.3) | 0.342 |
| Consumption of fruits/day | 1.0 (0.2) | 1.1 (0.2) | 0.032 |
| Days in a week of vegetables consumption | 6.9 (0.4) | 7.0 (0.3) | 0.029 |
| Consumption of vegetables/day | 1.5 (0.5) | 1.8 (0.4) | <0.001 |
| Mustard oil as a cooking oil | 376 (99.2) | 376 (99.7) | 0.574 |
| Amount of cooking oil a day (mL) | 11.6 (2.9) | 11.7 (3.3) | 0.599 |
| Amount of butter/ ghee day (*g*)[a] | 14.2 (33.4) | 4.7 (20.4) | <0.001 |
| Amount of salt while cooking/day (g)[a] | 7.9 (2.2) | 7.6 (2.1) | 0.051 |
| Salt > 5 g/d | 326 (86.0) | 315 (83.6) | 0.358 |
| Fried food consumption in a wk | | | |
| One | 251 (66.2) | 250 (66.3) | 0.976 |
| Two | 114 (30.1) | 114 (30.2) | 0.976 |
| Number of times fried food/day[a] | 2.7 (1.3) | 2.8 (1.3) | 0.239 |

*Data expressed as no. (%) or [a]mean (SD). Exposed group: birthweight>3500g; not exposed group: birthweight 2500-2999 g.*

**Table II Physical Activity and Anthropometric Assessment of Rural Cohort of Himachal Pradesh**

| *Characteristics* | *Not exposed (n=379)* | *Exposed (n=377)* | *P value* |
|---|---|---|---|
| Physical activity | | | |
| Indoor playing | 281 (74.1) | 293 (77.7) | 0.247 |
| Daily | 252 (66.5) | 280 (74.3) | 0.018 |
| Time (min/d) | 123.9 (87.0) | 138.9 (82.2) | 0.015 |
| Outdoor playing | 377 (99.5) | 372 (98.7) | 0.244 |
| Daily | 335 (88.4) | 334 (88.6) | 0.931 |
| Time (min/d)[a] | 157.5 (62.0) | 156.6 (51.9) | 0.816 |
| Physical sports at School | 54 (14.2) | 52 (13.8) | 0.857 |
| Time (min/d)[a] | 30.4 (4.3) | 31.7 (5.8) | 0.539 |
| Fraction of time played Indoor | 38.4 (24.3) | 42.5 (24.2) | 0.020 |
| Anthropometry,[a] | | | |
| Height (cm) | 118.8 (9.3) | 123.7 (8.3) | <0.001 |
| Weight (kg) | 20.3 (4.6) | 23.9 (6.0) | <0.001 |
| BMI (kg/m$^2$) | 14.1 (1.9) | 15.3 (2.7) | <0.001 |
| Percent of body fat | 8.5 (2.4) | 10.0 (3.9) | <0.001 |
| BMI *z*-score | | | |
| -3SD | 98 (25.9) | 69 (18.3) | 0.011 |
| -2SD | 133 (35.1) | 106 (28.1) | 0.023 |
| -1SD | 96 (25.3) | 98 (26.0) | 0.825 |
| At median | 36 (9.5) | 49 (13.0) | 0.128 |
| +1SD | 13 (3.4) | 35 (9.3) | <0.001 |
| +2SD | 3 (0.8) | 16 (4.2) | <0.001 |
| +3SD | 0 (0.0) | 4 (1.1) | 0.040 |

*Data expressed as no. (%) or [a]mean (SD). Exposed group: birthweight>3500g; not exposed group: birthweight 2500-2999 g.*

(vegetables and fruits) were included to assess adjusted measures of association. This study had a few limitations as well like we relied on proxy measures like indoor and outdoor games as a measure of physical activity. Also, failure to collect information on intrauterine growth and maternal nutrition posed a limitation to the measurement of association. Additional information on consumption of baked goods/biscuits, sugar-sweetened beverages, etc. could have been more informative. The education of the mother could have been associated with BMI, but for the study purpose, the socioeconomic status was assumed to be a more useful covariate for BMI after the age of six years.

In a hospital-based study [8], children with high mean birth weight had associated decline in physical growth in their first two years of life [8]. This was different from current study that was community-based and observed children from 7 to 10 years of age. Factors like physical activity and nutrition in later part of childhood were potential confounders in this study. The risk of obesity stayed significant as a measure of association for birth weight category and BMI after adjusting these covariates.

The available evidence from India suggests that the large size at birth and high birth weight predict high fat and lean body mass at the age of 6 years [14], and a high postnatal size at the age of 9 years [15]. Pooled analysis of five birth cohorts in low-and middle-income countries (LMICs) observed a positive significant association between high birth weight and BMI (OR 95% CI: 1.3; 1.2-

**WHAT IS ALREADY KNOWN?**

- High birth weight observed to be associated with high body mass index (BMI) among children based upon evidence observed mostly form hospital-based and cross-sectional studies.

**WHAT THIS STUDY ADDS?**

- Study adds to the literature a significant positive association between high birth weight and high BMI among children in rural areas.

1.3) [16]. Similarly, a 12-country cross-sectional study on children from 9-11 years of age observed a positive association between birth weight and BMI. Multivariable adjusted odds (95%CI) for BMI ( ≥ +2SD) was observed to be 1.5 (1.1-1.9) and 2.1 (1.5-2.9) among children with birth weight 3500-3999 and >4000 g, respectively [4]. A population-based study among children of age from 6 to 10 years observed that the risk of being overweight increases with each unit increase in birth weight for both boys and girls [17]. Low birth weight was associated with a decreased risk for overweight [18], and high birth weight (>4000 g) with a higher risk (1.7-1.8) of childhood obesity [18,19]. However, a recent meta-analysis did not observe any signi-ficant association between weight gain and childhood obesity in children born as small or appropriate for gestation age [20].

Focusing on childhood obesity is important to develop early intervention, as it is associated with adulthood obesity [21]. Childhood obesity is a major public health concern with increased risk for cardio-vascular disease, hypertension, type-2 diabetes mellitus and metabolic syndrome [22,23], with obesity during adolescence [24]. An increase in BMI during adolescence had increased risk of adverse metabolic profile in adulthood [25].

The study presents findings in community-based rural settings of 22 villages in the northern part of India. Most of the community-based birth cohort studies in India were from villages in the vicinity of a metropolitan/large city of Sothern India where the current one is far from any large city. The current study also reflects diversified dietary and physical activity pattern of the northern part of rural India compared to other parts of the world and India.

To conclude, high birth weight (>3500 g) was observed with an increased risk of childhood obesity and decrease the risk of undernutrition (BMI < -2SD) in rural areas among children of 7 to 10 years of age. In the study area, undernutrition was observed more than overnutrition along with consumption of fried foods. The dual burden of under- and over-nutrition could be addressed by observing trend of risk factors with a specific focus on at-risk children. A population-based approach to interventions focusing on healthy foods and physical activity will have the potential to address both under- and over-nutrition.

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RESEARCH PAPER

# Effect of Obesity on the Recovery Profile After General Anesthesia in Children: *A Prospective Cohort Study*

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**Background:** Obesity has become a serious problem not only in adult patients but also in pediatric patients.

**Aim:** To evaluate whether obesity affects the recovery profile after general anesthesia in children.

**Participants:** 40 children (aged 2–12 years) who underwent surgery under general anesthesia and had an American Society of Anesthesiologists (ASA) physical I and II.

**Methods**: This prospective cohort study was conducted over a period of 3 months (January- April, 2021). The patients were divided into two groups according to body mass index (BMI): Group I comprised obese children (BMI ≥95th for age percentile) (*n*=20) and Group II comprised children with a normal BMI (25–75th for-age percentile) (*n*=20). Anesthesia induction and maintenance were performed as per standard guidelines in both the groups.

**Outcome**: The recovery profile was evaluated with the following parameters: time to spontaneous ventilation, laryngeal mask airway removal time, time to open eyes, and post-anesthesia care unit discharge time.

**Results:** When the recovery profiles were compared, no significant differences were found between the groups. Time to spontaneous ventilation [mean difference (95% CI); 0.66 (0.09-1.42); *P*=0.085], laryngeal mask airway removal time [MD (95% CI); 1.12 (0.06–2.22); *P*=0.057), time to open eyes [MD (95% CI) 0.66 (0.40–1.74); *P*=0.217], and post-anesthesia care unit discharge time [MD (95% CI) 3.60 (0.59-7.25); *P*=0.054] were higher in Group II; however, these differences lacked both statistical and clinical significance.

**Conclusion:** The results suggest that obesity has no effect on the recovery profile after general anesthesia in children in our setting.

**Keywords:** *Adverse events, Body mass index, Outcome, Sedation*.

**Trial registration**: ClinicalTrials.gov; NCTO4652193.

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Obesity is having an increasing impact on adult patients undergoing surgery worldwide. Similar to this trend in adults, approximately one-third of children admitted for surgery are overweight or obese [1,2]. Childhood obesity is defined as a body mass index (BMI) above the 95th percentile for age and gender, and the prevalence of childhood obesity is upto 16.9% in some countries [3].

Obesity poses many difficulties for clinicians, as it is associated with pathophysiological changes affecting various organ systems [4,5]. Furthermore, obesity causes an increase in perioperative and postoperative anesthesia complications. Peripheral intravenous access difficulties caused by obesity and prolonged recovery profiles affect the patient care process [6]. Moreover, the greatest concern in anesthesia practice is the increasing adverse airway and respiratory events [2,6,7]. In addition, obesity increases hospital costs, length of hospital stays, and unexpected hospitalization rates after surgery [8,9]. Changes in body composition affect drug use; therefore, it is important to know the weight scales required for dosing in obese pediatric patients [10].

Although the perioperative care of obese adults has been extensively studied, relatively few studies of this type have examined obese children. Similarly; although, there are pediatric studies on the recovery profile, there are no studies on this issue in obese children. The present study aimed to evaluate the effect of obesity on the recovery profile of pediatric patients.

## METHODS

After obtaining institutional ethics committee approval, written consent was obtained from the legal guardians of the children enrolled in the present study, which was also registered at *http://clinicaltrials.gov.* Patients with cerebrovascular disease and a history of drug use affecting the central nervous system, as well as patients transferred to the ward without visiting the recovery room, were excluded from the study.

Patients included in the study were divided into two groups according to the body mass index (BMI): Group I comprised obese children (>95th BMI for age percentile), and Group II comprised children with a normal BMI (25–75th BMI for age percentile). For this division, reference values for Turkish children developed by Neyzi, et al. [11] were used by a pediatrician, using preoperative measurements that were blind to intraoperative and postoperative evaluations [11].

All patients enrolled in the study complied with the fasting periods specified by the ASA, and none of them received premedication. Standard monitoring was applied in the operating room. Anesthesia maintenance was performed with 1-2 minimum alveolar concentration (MAC) of sevoflurane in oxygen, which is the standard practice at our clinic. All baseline measurements were recorded before anesthesia induction. After face mask inhalation induction with 8% sevoflurane in oxygen in both groups, an intravenous catheter was placed, and fentanyl (2 µg/kg, intravenous) was administered. After the establishment of intravenous access, 5% dextrose, 0.45% NaCl, and 5-10 mL/kg/hour fluid infusion was initiated in accordance with our standard clinical practice. The sufficiency of anesthesia depth was evaluated considering the loss of eyelash reflex and jaw opening. Then, airway patency was provided through the laryngeal mask airway (LMA). Volume-controlled mechanical ventilation was applied after LMA insertion. Mechanical ventilation parameters were as follows: tidal volume (6-8 mL/kg), respiratory rates were adjusted to achieve an end-tidal carbon dioxide (EtCO2) of 30-35 mm Hg, and positive end expiratory pressure was not applied. Sevoflurane and remifentanil (0.25 µg/kg/min) was used for anesthesia maintenance. When there was a decrease of more than 20% in mean blood pressure compared to basal values, the crystalloid infusion rate was increased. If this was not enough, the concentration of sevoflurane was decreased, and anesthesia maintenance was continued. Paracetamol (10 mg/kg) was preferred for postoperative analgesia. Heart rate, mean blood pressure, and oxygen saturation (SpO2) values were constantly monitored and recorded at the following times: baseline, after induction of anesthesia, after successful LMA insertion, at the beginning of the surgical procedure, every 10 minutes during surgery, at the end of surgery, after LMA removal, and during eye opening with stimuli (verbal stimulus and/or painful pinching). Anesthesia maintenance stopped as the surgery neared conclusion. The LMA was removed when adequate depth of breathing was reached (tidal volume >6 mL/kg, respiratory rate >16 breaths per minute, and SpO2 greater than 98%) [12].

After removal of the LMA, the patients were transferred to the post-anesthesia care unit (PACU), where they were evaluated according to the following criteria for discharge: consciousness, normal vital signs, no pain, and no nausea or vomiting. Discharge from the PACU of all patients was performed by an anesthesiologist blinded to the study according to the standard guidelines in use in the institution. For measuring postoperative pain, the FLACC scale [13], which is based on a 0-10 score, was used in the PACU. According to the FLACC scale score, the patients' pain was evaluated as mild pain (0-3), moderate pain (4-7), and severe pain (>7). Postoperative nausea and vomiting was evaluated with the Baxter Animated Retching Faces (BARF) scale [14]. Surgical procedure duration, anesthesia time, and PACU stay time were also recorded. Anesthesia duration was evaluated as the time elapsed between induction of anesthesia and discontinuation of anesthetic agents. To evaluate the recovery profile, four parameters were evaluated: *i*) time to spontaneous ventilation (time elapsed between discontinuation of sevoflurane and remifentanil and initiation of spontaneous ventilation of the patient); *ii*) LMA removal time (time elapsed between discontinuation of sevoflurane and remifentanil and removal of LMA); *iii*) time to open eyes (time elapsed between discontinuation of sevoflurane and remifentanil and eye-opening in response to a verbal or painful stimulus); and *iv*) the length of stay in the PACU. The recovery profile was evaluated by two anesthetists experienced in pediatric anesthesia, and blinded to the patients' BMIs classification.

The current study was designed ($1-\beta=90\%$ and $\alpha=0.05$) to detect a 25% change in the time to spontaneous ventilation, as reported in a previous study [12]. We calculated a sample size of 16 patients for each group. Thus, considering a 25% possible loss, it was planned to include 20 patients in each group.

*Statistical analysis*: These were performed with SPSS 15.0 software (SPSS Institute). Student *t* test was used in the analysis of parametric data and results were presented as mean (SD) or mean (standard error of means). The analysis of categorical data was performed with the two-tailed Pearson chi-square test and the results were expressed as numbers. A *P* value less than 0.05 was considered statistically significant.

## RESULTS

A total of 40 patients were enrolled in this study between January, 2021 and April, 2021. All participants completed the study and none were excluded. Patients demographics are summarized in **Table I**. There were no significant differences between the two groups in terms of demographic data except weight ($P=0.004$) and BMI ($P<0.001$), which were higher in Group II.

**Table I Demographic Characteristics of the Study Groups**

| Characteristics | *Obese children* (*n*=20) | *Non-obese children* (*n*=20) |
|---|---|---|
| Age (y) | 6.90 (0.68) | 5.72 (0.78) |
| Male gender[a] | 15 (75) | 15 (75) |
| Weight (kg) | 25.62 (1.83) | 33.10 (3.08) |
| Height (cm) | 121.25 (4.13) | 113.25 (5.04) |
| Body mass index (kg/m$^2$) | 17.14 (0.29) | 24.18 (0.67) |
| ASA physical status I[a] | 18 (90) | 18 (90) |
| Anesthesia time (min) | 58.9 (1.56) | 55.2 (1.55) |

*Values are mean (95% CI) or [a]no. (%). ASA: American Society of Anesthesiologists.*

Changes in hemodynamic parameters are seen in **Fig. 1**. No change was made in the initial crystalloid infusion rate, as mean blood pressure did not decrease by more than 20% in both groups. There were no significant differences between measurement times.

Recovery times, FLACC, and BARF scale scores are summarized in **Table II**. There was no statistically significant difference in recovery times, FLACC, and BARF scale scores. Time to spontaneous ventilation, LMA removal time, time to open eyes and the length of stay in the PACU were higher in Group II; however, these differences did not have any statistical or clinical significance (**Table II**).

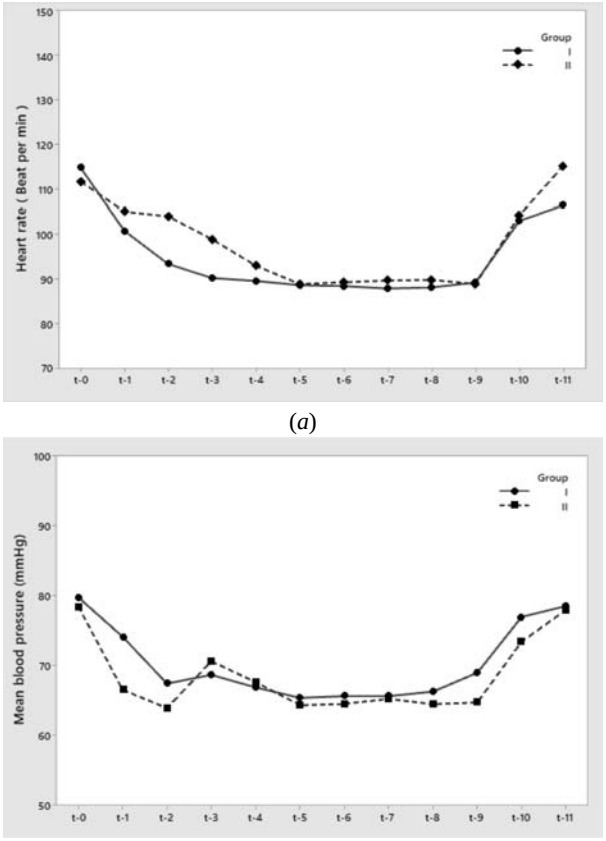


**Fig. 1** Changes in *a*) heart rate and *b*) mean blood pressure among obese (Group I) and non-obese (Group II) children undergoing general anesthesia.

## DISCUSSION

The results of the present study show that obesity has no effect on the recovery profile in pediatric patients. In studies evaluating children aged 2 years and older, it has been shown that critical adverse events such as difficult mask ventilation, difficult airway, difficult laryngoscopy, laryngospasm, and oxygen desaturation occur three times more frequently in obese children than non-obese children [2,6,7]. Two of these studies were prospective (observational and cohort, respectively) [2,7], and the other one was a retrospective study of 6094 patients [6].

Scherrer, et al. [15] reported that obesity is associated with an increased frequency of respiratory adverse events and delayed recovery in pediatric patients undergoing procedural sedation. Thirty-two institutions contributed data for this study during the study period, and 17.9% of 28,792 patients were found to be obese. However, the

**Table II Recovery Time, and Scores on the FLACC Scale and BARF Scale in the Two Groups**

| | *Obese children* (*n*=20) | *Non-obese children* (*n*=20) | *Mean difference* (*95% CI*) | *P value* |
|---|---|---|---|---|
| Time to spontaneous ventilation (min) | 3.57 (1.05) | 4.24 (1.31) | 0.66 (0.09-1.42) | 0.085 |
| LMA removal time (min) | 4.82 (1.18) | 5.94 (2.13) | 1.12 (0.06-2.22) | 0.057 |
| Time to open eyes(min) | 6.45 (1.40) | 7.12 (1.91) | 0.66 (0.40-1.74) | 0.217 |
| PACU stay time (min) | 23.35 (5.66) | 26.95 (5.76) | 3.60 (0.59-7.25) | 0.054 |
| FLACC scale scores | 3.45 (2.81) | 4.85 (2.72) | 1.40 (0.37-3.17) | 0.118 |
| BARF scale scores | 1.90 (1.60) | 2.30 (1.86) | 0.40 (0.20-1.90) | 0.248 |

*Values are mean (SD). PACU: Post-anesthesia care unit; BARF: Baxter animated retching faces; LMA: Laryngeal mask airway.*

**WHAT IS ALREADY KNOWN?**

- Obesity had no effect on the recovery profile after general anesthesia in pediatric patients with ASA Physical Status Classification I and II.

study was performed in patients who underwent procedural sedation, and the recovery profile was not clearlydelineated [15]. In a study conducted in obese adult patients using sevoflurane for maintenance of anesthesia, it was shown that obesity did not affect the recovery times [16]. In this study, recovery times were evaluated through bispectral index monitoring. In the present study, the recovery profile was defined by clinical parameters but the results were similar.

It has been shown that obesity causes a delay in the response to verbal stimuli and is associated with a prolonged return time in airway reflexes [17]. The patients in this study were older and two different inhalation anesthetics (sevoflurane and desflurane) were used randomly for the maintenance of anesthesia of the patients. In a retrospective study by Lee, et al. [18], in children aged 2-18 years, it was shown that obesity did not affect the duration of anesthesia. Of the 9522 patients whose data were available for the study, 17.2% were considered obese. In this study, the only independent predictor of both longer anesthesia and surgery durations was older age.

In a study that included morbidly obese children and adolescent patients undergoing laparoscopic surgery under total intravenous anesthesia, it was stated that excessive anesthetic administration was required and the emergence was prolonged [19]. This prospective study had; however, only included morbidly obese patients aged 9-18 years, which could have been the reason for the differences from this study.

There are only limited number of studies evaluating PACU discharge time in the literature, and the results are different from the results of our study [20,21]. In a study evaluating the effect of obesity degree on PACU discharge times in a pediatric patient group, it was stated that although PACU stay time was prolonged in both moderately and severely obese children who were operated under general anesthesia, there was no difference according to the obesity degree [20].

In a meta-analysis [21], it was shown that no difference could be detected between obese and non-obese adult patients when PACU discharge times were evaluated. These results are in parallel with the results of the present study. It was also stated in this meta-analysis that the choice of anesthetic agent had an effect on the PACU discharge times, and it was determined that the recovery after desflurane was faster than after sevoflurane, isoflurane and propofol [21]. However, due to the nature of the present study, sevoflurane was preferred for anesthesia induction and maintenance in pediatric patients. Although it is not clinically significant, we think that the high BARF score in Group II is the reason for prolonged PACU stay time in Group II. In a study conducted in adult obese population, the effects of opioid type (remifentanil, fentanyl and alfentanil) added to propofol on recovery profile were evaluated [22]. Spontaneous ventilation time and extubation times were found to be shorter in the remifentanil group compared to other opioids. In the present study, we preferred the use of remifentanil for anesthesia maintenance. In a meta-analysis on this subject, the effects of desflurane and sevoflurane on the recovery profile of patients undergoing bariatric surgery were compared, and it was stated that faster early recovery occurred in patients who used desflurane for anesthesia maintenance [23]. In another study comparing the effects of sevoflurane and desflurane on recovery profile in adult obese patients, no difference was found between the groups [24]. In our study, since our population consisted of pediatric patients, sevoflurane was preferred for the induction and maintenance of anesthesia.

There are some limitations of this study. Firstly, anesthetists evaluating the recovery profile could have an idea about the BMI of the patients based on their physical appearance; although, they were blind to the BMI category of the children. Secondly, BIS monitoring was not used to monitor the depth of anesthesia of the patients. However, this situation was eliminated by the use of the same clinical application in the maintenance of anesthesia.

In conclusion, based on the results of this study, we believe that obesity does not have any effect on the clinical recovery profile of pediatric patients operated under general anesthesia, and this information should inform routine clinical practice.

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RESEARCH PAPER

# Neighborhood Walkability Index and Its Association With Indices of Childhood Obesity in Bengaluru, Karnataka

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**Background:** The prevalence of childhood obesity is increasing in low-middle income countries like India. Built environment features such as walkability can influence weight-related outcomes but data from developing countries are scanty.

**Objective:** To develop population level walkability index in urban Bengaluru, and examine its association with indices of childhood obesity in school children.

**Study Design:** Nested cross-sectional study based on a cohort.

**Participants:** Normal healthy children aged 6 to 15 years from urban schools in Bengaluru. The children were stratified into different land use classification such as residential, commercial and open space based on residential address.

**Methods**: Anthropometric data, body composition data, measured using air displacement plethysmography.

**Outcomes:** Walkability index derived using residential density, street connectivity and land-use mix environment variables.

**Results:** The mean (SD) of age, body mass index (BMI), BMI *z*-score and percentage body fat (% Body fat) of 292 (50% boys) children were 10.8 (2.9) year, 17.4 (3.3) kg/m$^2$, -0.27 (1.35) and 20.9% (8.8), respectively. The mean (SD) walkability index was 16.5, which was negatively associated with BMI (slope -0.25 and -0.08) and percentage body fat (slope -0.47 and -0.21) for age 5 and 10 years, respectively in children, but the effects decreased with increasing age.

**Conclusions:** The findings of this pilot study suggest that the neighborhood walkability may be associated with the obesity indices in younger children. Future longitudinal studies are needed to understand how built environment affects health and body composition of children in India and other low-middle income countries.

**Keywords:** *Air displacement plethysmography, Body mass index, Built environment, Physical activity.*

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The increasing prevalence of childhood obesity is a major global public health challenge, steadily affecting the urban population in India, with combined prevalence of overweight and obesity of 5% in children aged 10-19 years [1]. In urban Bengaluru, 13% of school-going children were overweight, while 5% were obese [2]. Multiple lifestyle factors, genetic, behavioral and environmental conditions contribute to the etiology of obesity, also seen in Indian children [3]. The barriers to physical activity in children include lack of support/encouragement from parents, parental concerns with regard to safety, unsafe neighborhood, increased traffic, risk of accidents, inadequate built environment, and lack of recreational facilities [4]. Built environment can influence weight-related outcomes through physical activity, outdoor play, active transportation, dietary habits and sedentary behavior [5].

Neighborhood walkability, the capability to support walking for multiple purposes such as availing transport, shopping, recreation for children, commuting for school has shown to promote physical activity and prevent obesity [6]. Increased walkability characteristics have been associated with lower body mass index (BMI) *z*-score in children [7], and in adults [8]. Walkability index, defined as the extent to which the built environment is walking friendly, can be derived by adopting spatial data obtained from geographical information system (GIS), which has become popular to generate measures of specific attributes of the built environment, with its relative convenience, smaller measurement error, higher reliability, and ease of translating to into health and planning policy [9-11].

The need for optimal urban planning and transport policies to create and preserve built environments, with supportive infrastructure for active commuting such as walking and cycling has been highlighted by the World Health Organization's Global Action Plan for the Prevention and Control of NCDs 2013–2020 [12]. India is faced with multiple problems such as lack of supportive infrastructure, traffic congestion, overcrowded streets, air pollution and policies/ investments to promote active

commuting. There are limited Indian studies on neighborhood walkability and body weight [13].

Bengaluru is currently placed third among the top 10 fastest growing cities in the world [14]. The effect of urbanization on the prevalence of overweight/obesity among children is important. The primary aim of this exploratory study was to develop population level walkability index for selected localities in Bengaluru city. The secondary objective was to associate the walkability index with indices of childhood obesity such as BMI, body fat, and waist to height ratio (WHtR) in a subset of school children.

## METHODS

The Pediatric Epidemiology and Child Health (PEACH) cohort was established by the Division of Nutrition, St. John's Research Institute, Bengaluru in 2011 [15], and the children for the present study were recruited from this cohort from the year 2011 to 2016 [2]. The study was approved by the institutional ethics committee. Normal healthy children aged 6 to 15 years were included into the study, while children with any chronic illness as reported by the parents during the consenting process were excluded. The schools were selected by using convenience sampling procedure for operational feasibility.

The children of the above cohort were stratified into 12 land use classification typologies by combination of different degrees of land use of three basic patterns such as residential, commercial and open space based on children's residential address.

The anthropometric measurements of body weight, height and waist circumference were performed according to standard techniques [16]. Children were weighed in light clothing using a calibrated digital scale (Salter), to the nearest 0.1 kg. The height was measured to the nearest 0.1 cm using mobile stadiometer (Seca 213). Waist circumference (WC) was measured with a non-stretchable tape by trained nutritionists (exerting the same standard pressure on the tape) at the midpoint of the lowest rib cage and the iliac crest, to the nearest 0.1 cm, in a standing position during end-tidal expiration. The body fat of the children was measured using the BOD POD (Cosmed), with software version 5.2.0, which works on the principle of air-displacement plethysmography (ADP) [17]. The BOD POD was placed inside a van and parked at a location close to the measurement room in the school. The internal CV of body fat by this method was 2.3% [2]. All the other measurements were performed at the schools in a room allotted for the study.

Two frequently used GIS based walkability indexes are the South Australian Physical Activity in Localities and Community Environments (PLACE) study [10] and North American Neighbourhood Quality of Life Study (NQLS) [9] walkability indexes. These walkability indexes are constructed by four built environment variables-residential density; street connectivity; land-use mix; and net retail area (a measure of pedestrian friendliness). However, retail area (which is the measure that calculates the retail floor area in relation to the total amount of land area for retail use) information of Bengaluru city was not available electronically in public domain. Therefore, we derived GIS based walkability index in the present study using the other three components (**Web Fig. 1**).

The Global positioning system (GPS) coordinates of residential addresses of 300 students were obtained by Google earth or Open street map from the street level addresses. Further, these GPS coordinates were plotted on open street map to check the accuracy manually by street addresses of the residences and corrected accordingly in case of discrepancy. A buffer of 1 km radius was drawn over each of the residential coordinates within ArcGIS platform [18].

Dwelling density, street connectivity and land-use mix were then derived for each of the buffer from ArcGIS tools. The number of residential units were counted within each buffer from the detailed map of Bengaluru city obtained from the local municipality, over total residential area within the buffer. The dwelling density was derived by dividing number of residential units by total residential area within each buffer. The street connectivity was measured by street intersection density. With the help of Bengaluru map, the number of street intersections were counted within each of the buffer. Further, dividing the same by area of each of the buffer provided intersection density as a measure of connectivity.

Four different land use classifications that defined the variation of the land use such as residential, commercial, park and open space area, and public and semi-public area were measured. The sum of land area by the buffers was used to create an entropy score for each buffer, using the entropy equation [10]. The entropy equation results in a score of 0-1; 0 representing homogeneity and 1 representing heterogeneity.

In order to create a standard measure, all the above measures were converted into 10-point scale, with scores from 0 to 10 [10]. The walkability index was calculated by summing up the scores of dwelling density, connectivity and land-use mix; the calculated index would be between 0 and 30, with '0' being the worst and '30' being the best walkability.

Sociodemographic details of selected school going children such as age, sex, BMI, income of parent, parental

BMI along with body composition of the children were extracted from the original cohort data base.

*Statistical analysis*: Data were analyzed using statistical software R version 4.1.0 (R core team, 2021). Distribution of health and demographics along with walkability index were summarized by descriptive statistics. Univariate linear regression technique was applied to explore univariate association between BMI, body fat /obesity indicators and sociodemographic parameter. Unadjusted associations between obesity indices and walkability were also examined prior to the estimation of adjusted effects of walkability on obesity indicators. Finally, a multivariate linear mixed model with interaction was used to estimate the effects of walkability on obesity indices adjusted for relevant confounders, effect modifiers and cluster effects of school.

## RESULTS

The total cohort size was 9060 children (5172 boys). A stratified random sample of 300 children was selected from the cohort as per the land use classification (**Fig. 1**).

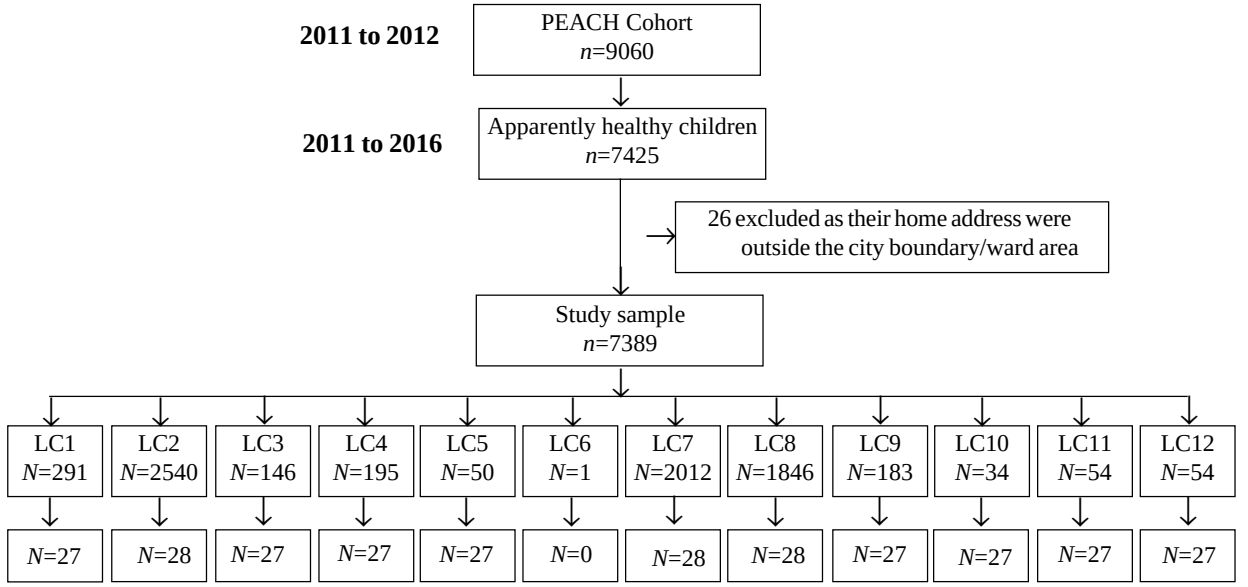
However, due to non-availability of body composition data of some of the selected children, the effective sample size was 292 (146 boys). Fifteen (5%) children were obese while 44 (15%) were overweight based on BMI *z*-scores. Only 260 households had complete family income data with mean family income INR 26000 to 30000 (USD 345 to 398) per month. The descriptive statistics are reported in **Table I**. **Web Fig. 2** depicts distribution of walkability across households of the study participants.

**Table I Demographic and Anthropometric Data (*N*=292)**

| *Variable* | *Mean (SD)* |
|---|---|
| Age (y) | 10.84 (2.89) |
| Body mass index (BMI) (kg/m$^2$) | 17.39 (3.26) |
| BMI *z*-score | -0.27 (1.35) |
| Waist-height ratio | 0.44 (0.06) |
| % body fat | 20.97 (8.78) |
| Body fat mass (kg) | 7.89 (5.23) |
| Paternal BMI (kg/m$^2$), *n*=243 | 25.17 (3.62) |
| Maternal BMI (kg/m$^2$), *n*=250 | 24.97 (4.76) |
| Walkability index | 16.54 (5.87) |

*BMI: body mass index.*

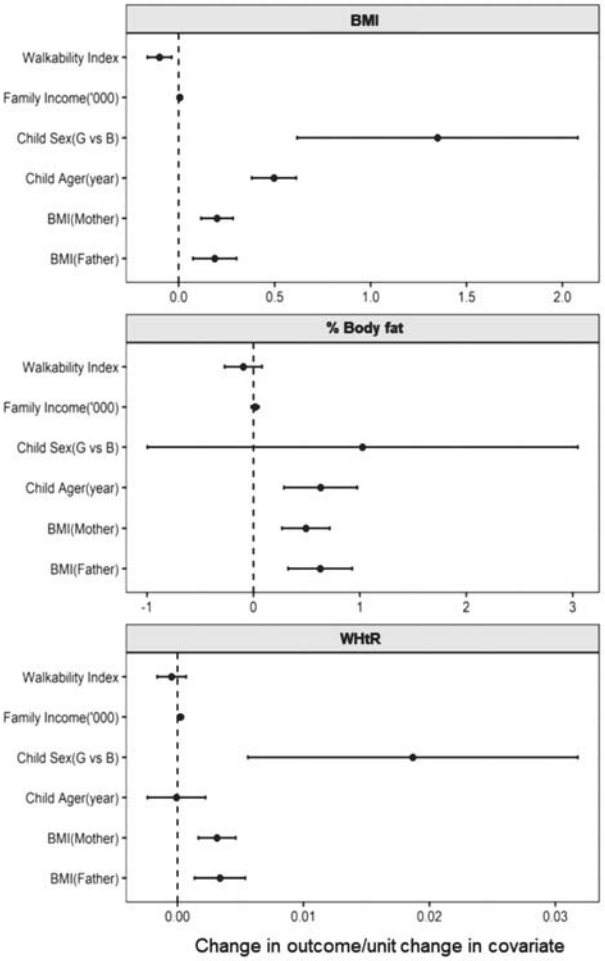
The univariate analysis exhibited significant association between BMI and walkability index, age, sex of the children and parental BMI. The walkability index showed negative associations with percentage body fat and waist height ratio (WHtR) but were not statistically significant (**Fig. 2**). In the present analyses, sex was considered as a confounder in the association of walkability with BMI and percentage body fat. When the association of sex with walkability index was analyzed in




A stratified random sample of 300 children were selected from the cohort. Out of 12, LCs, LC6 was excluded due to poor representation. Children were equally stratified into 11 land use classification (27 in each. 3 additional children were selected from the 3 biggest strata.

*LC=Land use classification*

**Fig. 1** Selection of study participants.




*Vertical dotted lines indicate the null hypothesis values. The error bars that do not intersect dotted lines were considered statistically significant.*

**Fig. 2** Univariate analysis between *a*) body mass index (BMI), *b*) % body fat and *c*) Weight-height ratio (WHtR) and walkability index, age and sex of the children, parental BMI (the error bar plots compare the unadjusted effects of different covariates and walkability on obesity indicators).

the regression model by using sex as an interaction term, we observed nonsignificant interaction coefficient, suggesting that there was no effect modification by sex.

The multivariate linear mixed effects with age interaction model that adjusted for sex, family income, parental BMI and cluster effects of schools showed a significant reduction in BMI with increase in walkability index, but the impact decreased with age (**Table II**). The slope of BMI as per age of a child was -0.415+0.033×age in years. Similarly, the slope of percentage body fat with respect to age was -0.723+0.051× age (years). The WHtR did not show any significant associations in the multivariate analysis (**Web Fig. 3)**.

**Table II Adjusted Estimates of Effect of Walkability on Obesity Indicators**

| *Outcome* | *Exposure* | *Change in outcome/ unit change in walkability* |
|---|---|---|
| BMI | WI | -0.41460 (-0.52501, -0.30418) |
| | WI ×age | 0.03304 (0.02547, 0.04060) |
| WHtR | WI | -0.00198 (-0.00422, 0.00027) |
| | WI ×age | 0.00011 (-0.00005, 0.00026) |
| % Body fat | WI | -0.72318 (-1.04723, -0.39913) |
| | WI × age | 0.05108 (0.02851, 0.07366) |

*Values are in slope (95 % CI). BMI-body mass index; WHR-waist-height ratio; WI-walkability index.*

## DISCUSSION

The present study developed population level walkability index for selected localities in Bengaluru and examined its association with indices of obesity in school going children. Walkability index is a quantifiable index to study health-promoting effects of the built environment that was negatively associated with the BMI and percentage body fat of children.

Studies from other countries have shown mixed results in the associations between walkability and childhood obesity [19-21], which could be due to difference in analytical methods, measurement of study variables like BMI, self-reporting of weight and height, and cross-sectional nature of the studies. However, the concept of an anti-obesogenic environment, including improved walkability is plausible. Additionally, the results from Western countries cannot be inferred for a LMIC like India, where the built environment has distinct patterns of urbanization, density, and land use. With the rapid increase in the prevalence of childhood overweight/ obesity and adult non-communicable diseases, it is important to understand the associations and develop country-specific solutions for India.

Walking is a significant mode of transport in India, but the difficulties faced by the pedestrians are lack of side-walks, disappearing zebra crossings, traffic and ongoing road constructions/repair work [22]. Only 38% of young adolescents and 17% of children in India were found to achieve the recommended 60-minutes/day of moderate-to-vigorous intensity physical activity (MVPA) duration [3]. Differences in physical activity between gender, socio-economic status and type of school (public vs private) have also been observed in Indian children [23,24].

The present study observed the effects of walkability index on BMI and percentage body fat to decrease with age. While the exact reason for this is not clear,

**WHAT IS ALREADY KNOWN?**

- Built environment features such as walkability can influence weight-related outcomes.

**WHAT THIS STUDY ADDS?**

- The present study developed population level walkability index for selected localities in Bengaluru
- Walkability index was negatively associated with the body mass index and percentage body fat of children.

psychosocial factors like social support from peers affected the associations between the built environment and active commute from schools (ACS) among adolescents [21]; adolescents chose the mode of transport to school based on ACS [21]. Younger children may not have the freedom for independent decision for walking plus ACS. Additional postulated reasons could be time spent in active games, academic pressure, increased mobile phone, screen and sedentary time duration and dietary habits, which were not evaluated in this analysis.

The limitations of the study included small sample size, cross-sectional study design and lack of objective assessment of physical activity. The lack of information on the retail area of Bengaluru city in the public domain limited the inclusion of this parameter while calculating the walkability index, which might have affected its accuracy. We anticipate that the true walkability index as defined previously [9,10], would have been adequately captured by the modified index of this study, as it considered three out of four domains. The lack of data on clear classification of land use patterns was another limitation. Data on facilities in the neighborhood like recreational facilities or food outlets were not captured. Future studies in India and other LMICs need to be planned, keeping in mind the limitations of non-availability of relevant data in LMICs. Large scale studies with multilevel approach examining the neighborhood effect on individual-level health outcomes are needed.

In conclusion, this pilot study suggests that the neighborhood walkability is associated with the obesity indices in younger children and can be a catalyst for future longitudinal studies examining the associations of walkability with weight-related behaviors and outcomes. Future studies need to look into the individual components of walkability and built environment to understand how environment and health interact in an LMIC country like India.

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*Ethics clearance*: IEC, St John's Medical College Institutional Ethical committee; No. 177/2008, dated Feb 05, 2009.

*Contributors*: DP: data acquisition, preliminary analysis, interpretation of data, writing original draft; SG: methodology, formal analysis, interpretation of data, writing-review and editing; RK: conceptualization, supervision, analysis, interpretation of data, writing – critical reviewing and editing.

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*Note*: Additional material related to this article is available at *www.indianpediatrics.net*

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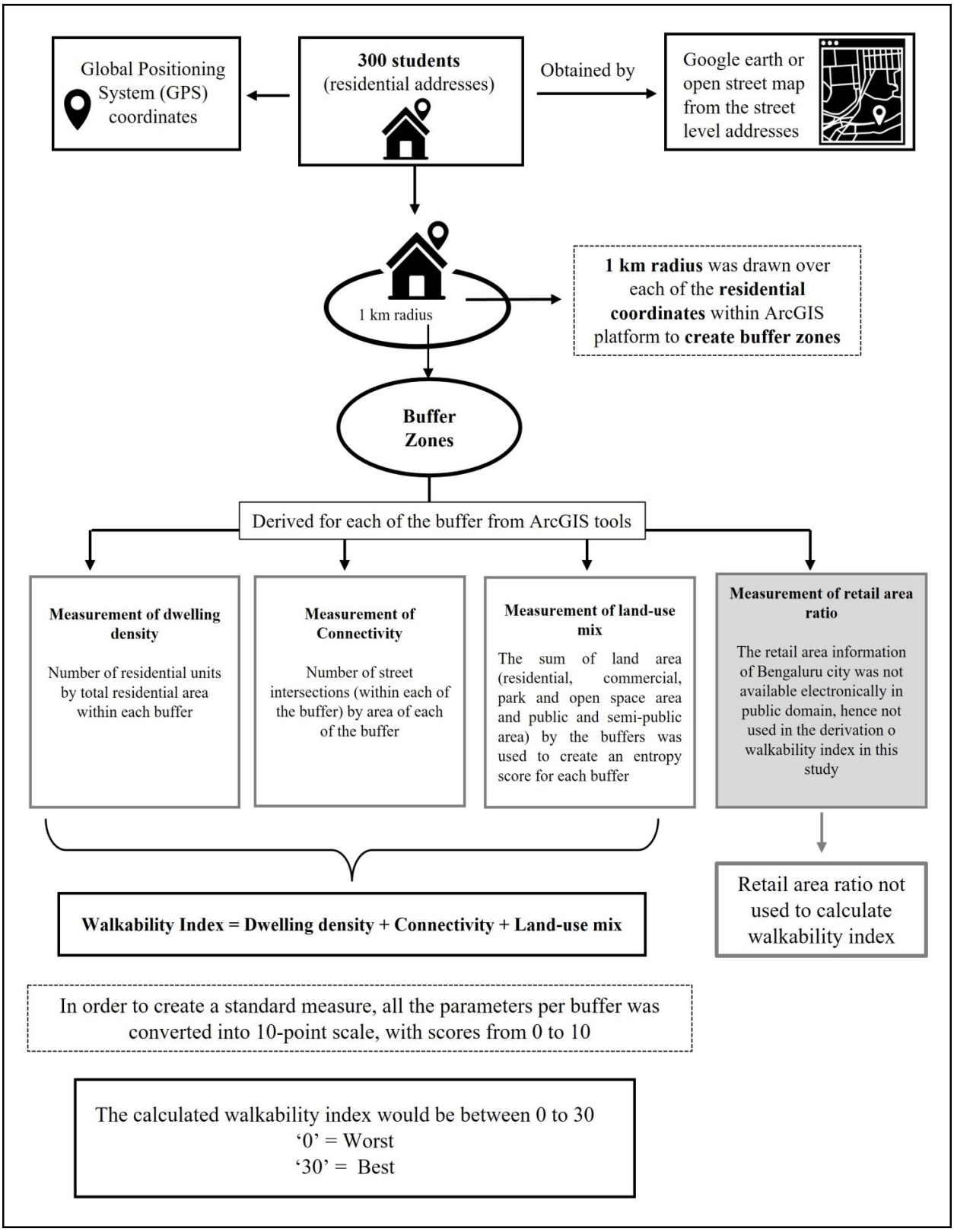
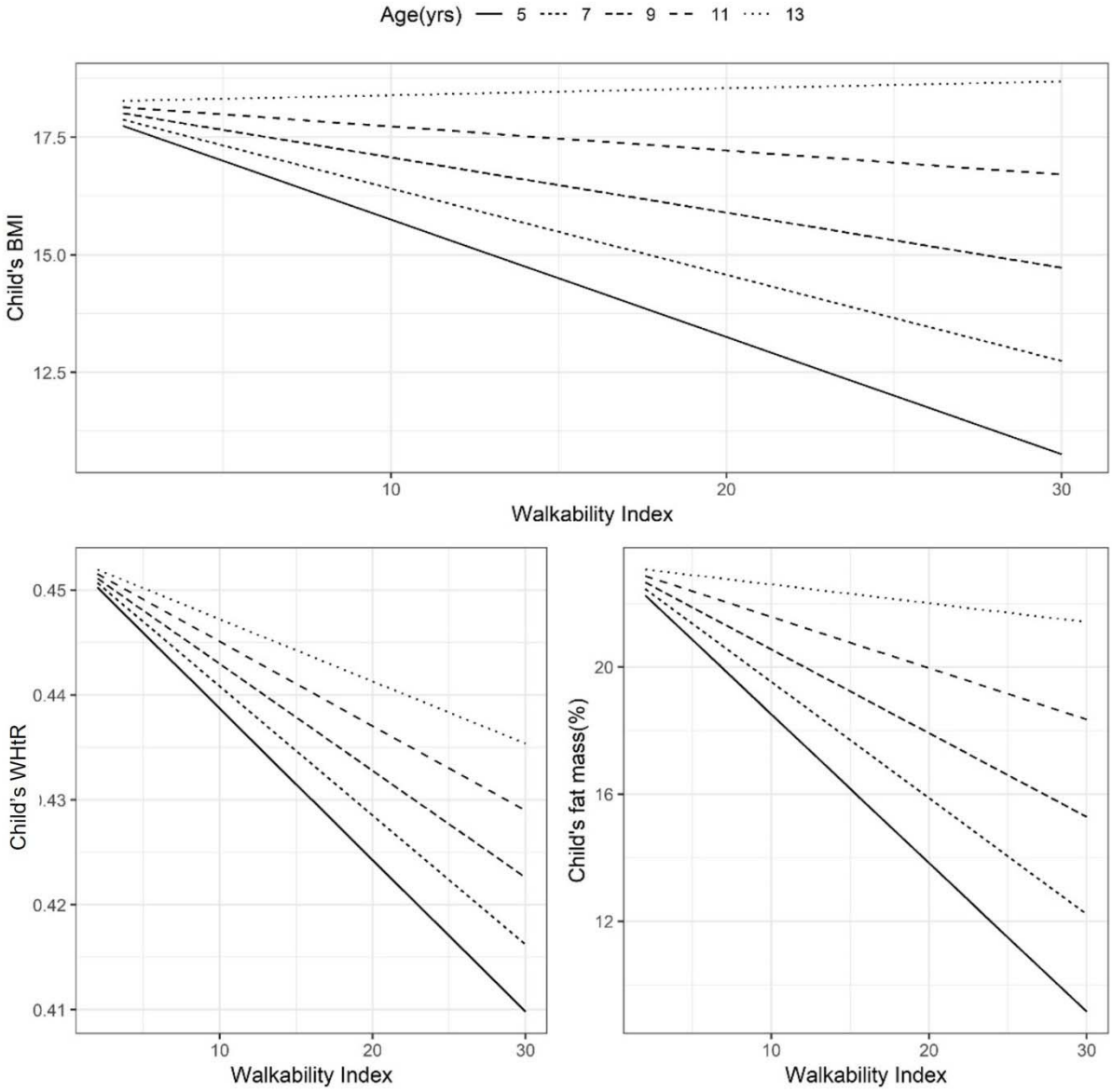
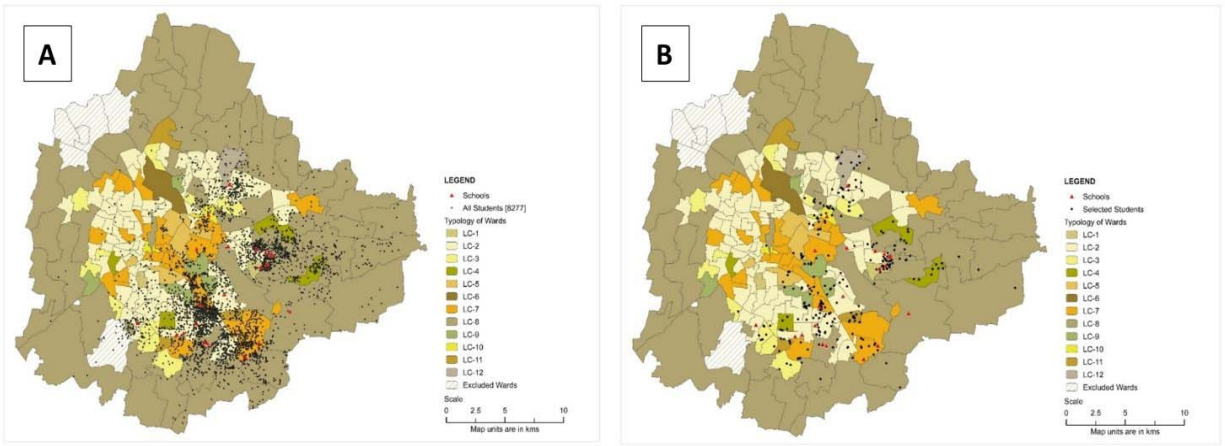



**Web Fig. 1** Calculation of Walkability index.




**Web Fig. 2** Multivariate mixed effects model with age interaction.

[The multi-panel plot shows how the impact of walkability on obesity indicators decreases with increasing age. In the multivariate regression, age was included as an interaction term with walkability index. The slopes at different age were estimated by regression coefficient of walkability index and coefficient corresponding to interaction of age and walkability index by $\beta = \beta_{WI} + \beta_{WI \times age} \times age$; while $\beta_{WI}$ & $\beta_{WI \times age}$ were obtained from regression model specified in method section].




**Web Fig. 3** Panel A shows the distribution of residential address and schools of PEACH cohort participants across Bengaluru city. Panel B shows the distribution of the residential address and schools of the participants selected from the current study.

RESEARCH PAPER

# Risk Factors of Cooking-related Burn Injury Among Under-Four Children in Northwest Ethiopia: *A Community-Based Cross-Sectional Study*

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**Objective:** To investigate the prevalence and risk factors of cooking-related child burn injury. **Methods:** A cross-sectional community-based study was conducted among a total of 5830 children with their respective caretakers in randomly selected 100 clusters. Data were collected through face-to-face interviews using a structured questionnaire. Logistic regression was used to identify the risk factors and adjusted odds ratios were used as measures of effect. **Results:** The prevalence of cooking-related child burn injury was 6.2% (95% CI: 5.5-6.8). This burden was linked with risk factors such as lower literacy of caretaker, family size, using traditional cook stove, long cooking time, and presence of extra indoor burning events as well as lack of separate kitchen, child supervision, and injury prevention awareness. **Conclusion:** Children experience a high burden of burn injury. Thus, stakeholders should work to reduce this burden by controlling the aforementioned risk factors.

**Keywords:** *Prevention, Scalds, Unintentional injury*.

Cooking-related burns create a major public health burden in low- and middle-income countries (LMICs), where over 95% of burn deaths occur [1], and this type of injury carries greater long-term morbidity than burns of any other type [2]. The global burn registry report by the World Health Organization (WHO) shows that, burn injury incidence is excessively concentrated in LMICs [3,4]. Children, especially those under five years of age, are more vulnerable to experienc-ing pediatric burns [5], and several studies have revealed that most pediatric burn injuries occur below the age of 4 years [6-8].

In Ethiopia, burn injury is a common public health problem [9,10], and usually occurs in domestic kitchens [8,11]. However, there is only little population-based information in the East African region [12], with only a few studies reporting on the determinants of child burn injuries in Ethiopia [13]. Therefore, this study aimed to investigate the prevalence and risk factors of cooking-related child burn injury.

## METHODS

A cross-sectional study was conducted in Mecha District, Northwest Ethiopia. The majority of the households in the study localities primarily use an open three-stone traditional type cook-stoves for cooking on ground level. Besides, improved cookstove types are alternatively used by the community in the study area [14,15].

The sample size was calculated assuming a 95% confidence level, a 3% acceptable margin of error, 13% estimated population proportion of child burn injury in Ethiopia, a design effect of 2 for cluster sampling, and an addition of 5% to account for any unpredictable events. The final sample size was estimated to be about 1017 children with their respective caretakers. Neverthe-less, to achieve the benefit of having a larger sample size, which would increase the accuracy of estimations by decreasing the sampling error, we included all the 5830 eligible children from the wider cookstove trial project [14].

From the total of 132 clusters in the study area, 100 clusters were chosen randomly by the lottery method. Then, all eligible children with their respective caretakers were included in the study. However, when two or more eligible children were found living in the same household, only the youngest child was included. Also, in situations where there were two or more burn injury events on a single child, only the latest injury was considered, to reduce the possibility of recall bias.

We defined cooking-related child burn injury as the occurrence of cooking-induced child burn injury related to the actual household cooking practice in the last 12 months, as assessed by the local nurses through face-to-face interviews. Burn injury mechanism was classified as burns from hot liquids (scalds), burns from flames, burns from hot solid objects (contact burns), and others. Also,

the severity of the burn was defined as light (no scar), moderate (scar smaller than a coin), and serious (scar larger than a coin). Similarly, the predictor variables were defined and assessed as fully mentioned in the attached document (**Web Appendix I**).

Data were collected from 1- 31 May, 2018 by 15 trained local nurses through face-to-face interviews using a pre-tested questionnaire. The occurrence of burn injury within the last 12 months was assessed by asking the primary caretakers whether the child had a burn injury related to the household cooking practice, as well as through examining the injured child by trained nurses using the child burn management guideline [16].

*Statistical analysis:* To evaluate the effect of possible predictor variables on the occurrence of child burn injury, initially, univariate logistic regression analyses were carried out to observe the independent association of child injury with each predictor variable independently. All variables with a *P* value of 0.2 and below in the single model analyses were entered into a multivariable logistic regression analysis model to describe the associations between child injury and predictor variables.

## RESULTS

A total of 5830 eligible study participants were included in the study (**Fig. 1**). The majority (92.1%) of the household used a traditional type of household cook stove (**Table I**).

The prevalence of cooking-related child burn injury that occurred in the past 12 months was 6.2% (95% CI: 5.5-6.8). Its distribution by gender was 6% (95% CI: 5.1-6.9) for females and 6.3% (95% CI: 5.4-7.2) for males and an elevated injury prevalence (12.5%) was observed in ages between 36-47 months of life. More than one-third (37.6%) of the injuries were moderate in severity and the common mechanism of injury was burning from hot liquids (34.5%), and occurred largely (46.2%) in the evening time (**Web Table I**).

The burden of child burn was linked with various risk factors such as lower literacy status of caretaker [AOR (95% CI) 2.21 (1.05-4.67)], high family size/overcrowding [AOR (95% CI) 2.35(1.25-4.43)], lack of separate kitchen [AOR (95% CI) 2.19 (1.56-3.07)], using traditional cook stove [AOR (95% CI) (1.23-3.36)], lack of child supervision [AOR (95% CI) 2.27 (1.63-3.17)], lack of injury prevention awareness [AOR (95% CI) 1.65 (1.31-2.09)], and long cooking time [AOR (95% CI) 1.99 (1.31-3.04)] (**Table II**).

## DISCUSSION

The findings of this study reveal that 6.2% (95% CI: 5.5, 6.8) children had suffered from cooking-related burn injury in last one year. This finding is lower than the findings of two previous studies that reported a prevalence of 10%

**Table I Sociodemographic and Cooking-related Characteristics of Study Participants (*N*=5830)**

| *Characteristic* | *No. (%)* |
|---|---|
| Rural residence | 4366 (74.9) |
| Female gender | 2816 (48.3) |
| Age of child | |
| 0-11 mo | 1601 (27.5) |
| 12-23 mo | 1664 (28.5) |
| 24-35 mo | 1528 (26.2) |
| 36-47 mo | 1037 (17.8) |
| Literacy status[a] | |
| Does read and write | 4158 (71.3) |
| Read & write only | 452 (7.8) |
| Primary school (grade 1-8) | 474 (8.1) |
| Secondary school (grade 9-12) | 366 (6.3) |
| Higher education | 380 (6.5) |
| Occupational status[a] | |
| Farmer | 3893 (66.8) |
| Merchant | 839 (14.4) |
| Housewife | 496 (8.5) |
| Employee | 332 (5.7) |
| Daily laborer | 234 (4.0) |
| Student | 36 (0.6) |
| Family size | |
| 2-5 | 3183 (54.6) |
| 6-7 | 1784 (30.6) |
| 8-9 | 746 (12.8) |
| ≥10 | 117 (2.0) |
| Rooms in the house | |
| One | 1384 (23.7) |
| Two | 3203 (55.5) |
| Three | 1101 (18.9) |
| ≥4 | |
| Separate kitchen | 3685 (63.2) |
| Primary cookstove type | |
| Traditional stove | 5371 (92.1) |
| Improved stove | 459 (7.9) |
| Meals cooked per day | |
| ≤1 meal | 1090 (18.7) |
| 2 meals | 3366 (57.7) |
| 3 meals | 1008 (17.3) |
| ≥4 meals | 366 (6.3) |
| Time taken for cooking per day | |
| 1-2 h | 1505 (25.8) |
| 3-4 h | 3621 (62.1) |
| ≥ 5 h | 704 (12.1) |
| Cook stove extinguishing practice | |
| Extinguish each time | 1625 (27.9) |
| Extinguish only at night | 2470 (42.4) |
| Do not extinguish at all | 1735 (29.8) |
| Extra indoor burning events | 5583 (95.8) |
| Estimated time/day | |
| 1-2 h | 3622 (62.1) |
| 3-4 h | 544 (9.3) |
| 12 h | 1214 (20.8) |
| 24 h | 203 (3.5) |
| Not aware of child injury prevention[a] | 3009 (51.6) |

[a]*primary caretaker.*

**Table II Multivariate Analysis of Risk Factors Associated With Cooking-related Child Burn Injury in North West Ethiopia, 2018 (*N*=5830)**

| *Characteristics* | *Crude OR (95% CI)* | *AOR (95% CI)* |
|---|---|---|
| Urban residence | 0.55 (0.41,0.73) | 0.80 (0.47,1.35) |
| Female | 0.95 (0.77,1.18) | 0.94 (0.76,1.18) |
| Age[b] | | |
| 1 year | 2.236 (1.52,3.28) | 2.13 (1.44,3.15)[i] |
| 2 years | 2.87 (1.97,4.17) | 2.81 (1.91,4.12)[i] |
| 3 years | 5.74 (3.98,8.29) | 5.87 (4.03,8.57)[i] |
| Does not read and write[a,c] | 3.14 (1.60,6.14) | 2.21 (1.05,4.67)[i] |
| Occupational status[a,d] | | |
| Student | 2.16 (0.61,7.66) | 4.27 (1.06.17.21)[i] |
| Total family size[e] | | |
| 8-9 | 2.45 (1.67,3.59)[i] | 1.79 (1.18,2.72) |
| ≥10 | 4.30 (2.40,7.68)[i] | 2.35 (1.25,4.43) |
| No child supervision by caretaker | 1.29 (1.04,1.60) | 2.27 (1.63,3.17) |
| No awareness on prevention[a] | 1.84 (1.47,2.30) | 1.65 (1.31,2.09) |
| Cooking area inside living house | 1.30 (1.06,1.61) | 2.19 (1.56,3.07) |
| Traditional stove | 1.57 (1.98,2.51) | 2.04 (1.23,3.36) |
| Meals cooked per day[f] | | |
| 3 meals | 1.88 (1.31,2.69)* | 1.91 (1.28,2.83)[i] |
| ≥4 meals | 2.36 (1.52,3.66)* | 1.98 (1.23,3.18)[i] |
| Length of time taken for cooking per day[g] | | |
| 3-4 h | 2.52 (1.82,3.48)* | 1.98 (1.22,3.21)[i] |
| ≥5 h | 3.09 (2.07,4.62)* | 1.99 (1.31,3.04)[i] |
| Do not extinguish cook stove[h] | 3.03 (2.18,4.20)* | 1.60 (1.04, 2.46)[i] |
| Child spends some time near cook stove | 2.34 (1.43,3.84) | 1.78 (1.05,3.03)[i] |
| Extra indoor burning event | 3.28 (1.34,7.99) | 2.68 (1.08,6.68)[i] |

*[a]primary caretaker; [b]compared to <1-year-old; [c]compared to higher education; [d]compared to housewife; [e]compared to 2-3 member household; [f]compared to ≤1 meal/d; [g]compared to 1-2 h/d; [h]compared to extinguishing each time. [i]P<0.05.*

among children younger than 18 years in Northwest Ethiopia [17], and a national prevalence of 13% among children younger than 14 year in Ethiopia [11]. The possible justification for this disparity might be the difference in the age range of study participants, as the age of our study participants was under four year.

Concerning the risk factors, the risk of child burn injury was significantly increased by more than five times (AOR=5.74) among 3-year-old children as compared to less than one-year-old children. This could be because younger children have more intimacy with their caretakers during cooking, which put them at greater risk of unintentional burn injury exposure. The risk of burn injury was significantly elevated among children whose caretakers did not read and write. This finding is comparable to a previous study, which found a positive association between better educational level of caretakers and child injury reduction [17].

The risk of child burn was also increased among children living in households with a family size of 10 or more. This result can be explained by the fact that living in overcrowded households may increase the risk of burn injury among young children by creating a cluttered situation in the home. Also, overcrowded households might not have adequate space for cooking and playing for toddlers. The risk of childhood burn injury was also increased among children living in households with a cooking area located inside the main living house. Correspondingly, a separate kitchen is one of the most recommended types of solutions to minimize the risk of fire hazards [18].

Among the behavioral factors, lack of child supervision by a caretaker was significantly linked with a greater risk of child burn injury. This result is comparable with the finding of a previous study [19], which reported that lack of caretaker supervision was the major determinant factor for burns among Ethiopian children.

Recall and social desirability biases could be a potential limitation for a survey of this kind. This investigation could be also subjected to the limitations of a cross-sectional study design and cluster sampling method. The results of this study, which underscored already well-recognized risk factors of child burn injury in this region, will guide both the policy makers for interventions aimed at addressing this common cause of childhood morbidity.

*Ethics clearance*: Ethical Review Committee, College of Medicine and Health Sciences at Bahir Dar University; No. 088/18-04, dated April 4, 2018.
*Contributors*: MMA: was the principal investigator of the study and took the leading responsibility, starting from the origin, design, and supervising of the data collection process to the final data analysis and preparation of the manuscript. AA, TS: contributed, starting from the data analysis to the preparation of the manuscript and reviewing the final document. All authors approved the final manuscript.
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*Competing interests*: None stated.
*Note*: Additional material related to this study is available with the online version at *www.indianpediatrics.net.*

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**WHAT THIS STUDY ADDS?**

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**Web Table I Severity, Cause, and Time of Child Burn Injury Across Age-groups in North West Ethiopia, 2018 (*N*=5830)**

| *Characteristics* | *Age of child (mo)* | | | |
|---|---|---|---|---|
| | *0-11* | *12-23* | *24-35* | *36-47* |
| Severity of injury | | | | |
| Light (no scar), *n*=126 | 6 (15.4) | 26 (29.5) | 49 (48.0) | 45 (34.6) |
| Moderate (scar ≤ a coin), *n*=135 | 18 (46.2) | 45 (51.1) | 24 (23.5) | 48 (36.9) |
| Serious (scar > a coin), *n*= 98 | 15 (38.5) | 17 (19.3) | 29 (28.4) | 37 (28.5) |
| *Mechanism of injury* | | | | |
| Burns from hot liquids, *n*=124 | 9 (23.1) | 35 (39.8) | 33 (32.4) | 47 (36.2) |
| Burns from flames, *n*=106 | 10 (25.6) | 21 (23.9) | 37 (36.3) | 38 (29.2) |
| Burns from hot solid objects, *n*=113 | 19 (48.7) | 28 (31.8) | 27 (26.5) | 39 (30.0) |
| Others, *n*=16 | 1 (2.6) | 4 (4.5) | 5 (4.9) | 6 (4.6) |
| *Time of injury* | | | | |
| Morning, *n*=119 | 9 (23.1) | 23 (26.1) | 35 (34.3) | 52 (40.0) |
| Day time, *n*=74 | 7 (17.9) | 21 (23.9) | 19 (18.6) | 27 (20.8) |
| Evening, *n*=166 | 23 (59.0) | 44 (50.0) | 48 (47.1) | 51 (39.2) |

*Data in no. (%).*

***Web Appendix 1***

***Definitions, data sources, and methods of assessment for potential predictor variables***

The potential predictor variables were broadly categorized into socio-demographic, environmental, and behavioral variables. These variables were assessed through face-to-face interviews with the primary caretakers of the children by field nurses using questionnaires as well as through observations as fully mentioned next:

i. Socio-demographic variables

- Gender of child: The child's gender was assessed by asking the respondent as female or male.
- Age of child: The child's age was assessed by asking the respondent by classifying it into four categories as i] < 1-Year-old; ii] 1-Year-old; iii] 2 Years old, and iv] 3 Years old.
- Literacy status of primary caretaker: Refers to the level of education achieved by the primary caretaker in child burn injury reduction. To study the role of educational level in the occurrence of cooking-related child burn injury, primary caretakers were asked about the level of education they accomplished as assessed by classifying them into five categories as i] do not read and write; ii] read and write, iii] primary schooling completed, iv] secondary schooling completed, and v] higher education completed.
- Occupational status of caretakers: The occupational status of the primary caretaker was assessed by asking the respondent by classifying into six categories as i] Farmer, ii] Merchant, iii] Student, iv] Employee, v] Daily laborer, and vi] Housewife.

ii. Environmental variables: Five features of environmental factors were assessed.

- Setting of child's residence: Refers to the role of a residential setting in the occurrence of cooking-related child burn injury between rural inhabitant and urban dweller children and it was assessed by classifying into two categories as i] Urban and ii] Rural.
- Total family size of the household: Refers to the role of crowding on child burn injury as measured by the total number of individuals permanently living in the household, and it was assessed by classifying into four categories as i] 2-3 individuals, ii] 4-5 individuals, iii] 6-7 individuals, iv] 8-9 individuals, and V] 10 or more individuals (29).
- Number of rooms in the main living house: Refers to the role of adequate space inside the main living house in the occurrence of cooking-related burn injury among children through reducing or producing an injury-conducive environment as measured by the total number of rooms in the main living house. The total number of rooms was assessed by counting the number of rooms in the main living house by classifying it into four categories as i] one room, ii] two rooms, iii] three rooms, and iv] four or more rooms (29).
- Primary cookstove technology type: Primary cookstove type was considered in this study as assessed through asking and observing the primary cookstove technology type of the household by classifying it into two categories as a traditional or improved stove (28). The term improved stove refers to a household cookstove that is designed to use less fuel and reduce the volume of smoke produced compared to the traditional stove and the term traditional cookstove refers to an open-fire cookstove type constructed by household members for cooking purposes that are not energy-efficient and have poor combustion features (33).
- Location of cooking area: Refers to the role of the main cooking quarter location in child burn injury incidence as assessed through observing and asking respondents about the location of the main cooking quarter of the household by classifying it into two categories as i] Inside the living house and ii] Separate kitchen.

iii. Behavioral variables: the next listed behavioral factors were investigated in this study:

- Child supervision: Refers to the role of proper child supervision by primary caretaker in cooking-related child burn injury occurrence as assessed through asking the primary caretakers whether they are commonly available at home or not by classifying them into two categories as Yes or No.
- Awareness of primary caretakers on burn injury prevention: This refers to the role of primary caretakers' injury awareness in child burns injury prevention as assessed by asking respondents whether they are aware that cooking-related child burns injury is preventable or not by classifying into two categories as i] Cooking-related child burn injury is unavoidable, ii] Cooking-related child burn injury is avoidable.
- Number of meals cooked per day: Frequency of meals was assessed by asking respondents what was the average number of meals cooked per day by classifying it into four categories as i] one or less, ii] two meals, iii] three meals and iv] four or more meals.
- Length of time taken for cooking: Refers to the average amount of time families spend in cooking in hours per day which was assessed through asking respondents what was the average time taken for cooking in hours per day as classified into three categories as i] 1-2 hours, ii] 3-4 hours and iii] 5 or more hours per day.
- Cookstove extinguishing practice of households: This refers to the role of cookstove extinguishing practice of households between uses in the occurrence of cooking-related child burn injury as assessed by asking respondents whether they regularly extinguish their cookstove or not between uses by classifying into three categories as i] Extinguish each time, ii] Extinguish only at night, and iii] Do not extinguish at all.
- Child handling practice: This was assessed by asking caretakers whether their child regularly spent time near a cookstove within a 1.5-meter distance during cooking times by classifying it into two categories as Yes or No.

Extra indoor burning event. This refers to the presence of any extra burning event such as the burning of incense, coffee ceremony, local alcohol/ "areqi" making or cooking for business in the household that commonly occurs inside the main cooking quarter other than the customary cooking which may influence the occurrence of cooking-related child burn injury. It was assessed by asking and observing the presence of any extra indoor burning occasion inside a household by classifying it into two categories as Yes or No (28).

RESEARCH PAPER

# Neonatal Outcomes in Pregnant Women With Repaired and Unrepaired Congenital Heart Disease in Zhejiang, China

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**Objective:** To compare the neonatal outcomes in pregnant women with repaired vs unrepaired congenital heart disease (CHD). **Methods:** Data on pregnant women with CHD was retrieved from our hospital records for the duration April, 2014 to December, 2021. Pregnant women with CHD were divided into two groups: simple CHD and moderate-to-complex CHD. **Results:** In simple CHD group, neonatal outcomes were similar in pregnant women with repaired and unrepaired CHD. By contrast, in moderate-to-complex CHD group, the offspring of women with unrepaired CHD had lower gestational age [mean (SD) 34.3 (2.7) vs 36.8 (2.1) week; *P*=0.016] and lower birth weight [mean (SD) 2126.8 (711.9) vs 2720 (645.7); *P*=0.037] than those with repaired CHD. Infants of women with unrepaired moderate-to-complex CHD had a higher risk of premature delivery (87.5% vs 45.5%, *P*=0.013), low birth weight (81.3% vs 36.4%, *P*=0.04) and neonatal intensive care unit (NICU) admission (68.8% vs 27.3%, *P*=0.034). **Conclusions:** Surgical repair before pregnancy in women with moderate-to-complex CHD significantly minimized the risks of neonatal complications.

**Keywords**: *Cardiac intervention, Pregnancy outcome, Severity, Surgical repair*.

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With advances in surgical intervention and intensive care, more and more women with congenital heart disease (CHD) are surviving to childbearing age. Women desirous of pregnancy might face various challenges during pregnancy and child birth. For women with simple CHD, who are free of symptoms, pregnancy and delivery could be well tolerated [1], but for women with complex CHD, pregnancy presents a challenge with numerous alterations in cardiovascular physiology [2]. Pregnancy with CHD is associated with a high risk of premature delivery and small for gestational age (SGA) [3,4]. The risks of adverse neonatal events are influenced by types of cardiac defects and surgical repair. Women with complex CHD who undergo cardiac surgery, seem to well tolerate pregnancy, which may reduce the risks of neonatal complications. Data on benefits of aggressive surgical intervention before pregnancy with different severity of CHD are unknown. The present study was conducted to compare neonatal outcomes among women with cardiac surgery for CHD before pregnancy.

## METHODS

This was a retrospective study that retrieved records of women with CHD between April, 2014 and December, 2021 at First Affiliated Hospital, College of Medicine. The patients diagnosed with CHD and concurrent diseases such as pregnancy induced hypertension (PIH), antepartum hemorrhage (APH), pre-eclampsia, maternal anemia, nephropathy, liver disease, pulmonary disease, connective tissue disease, and with induced abortion were excluded. Data were collected using medical records. Information about mothers included age at inclusion, type of heart defects, prior surgical procedures, severity of disease as per New York Heart Association (NYHA) class, left ventricular eject fraction (LVEF), pulmonary artery pressure, oxygen saturation, gestational diabetes (GDM), thyroid function and drug exposures. Information about neonatal outcome, as obtained from the medical records, included gestational age at birth, type of delivery, birthweight, Apgar score and neonatal complications.

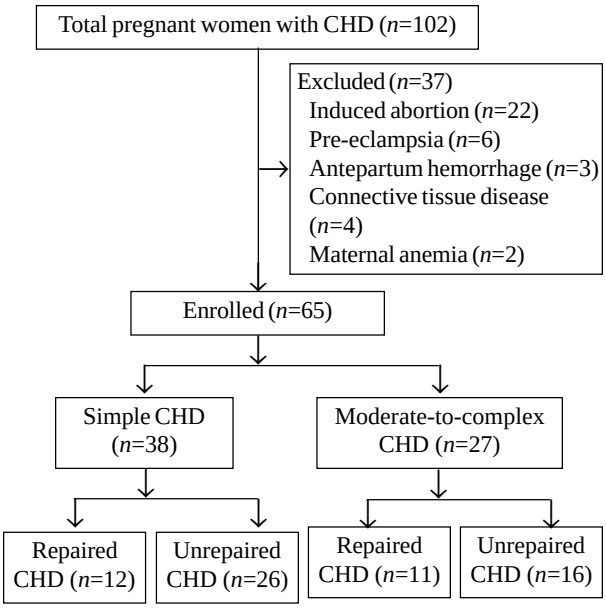
Based on guidelines from the European Society of Cardiology, isolated atrial septal defect (ASD), ventricular septal defect (VSD) and patent ductus arteriosus (PDA), were classified as simple CHD and other heart defects were considered as moderate-to-complex CHD [5]. Pulmonary arterial hypertension (PAH) was defined hemodynamically by the presence of a mean pulmonary artery pressure of at least 25 mmHg with a pulmonary capillary wedge pressure or left ventricular end diastolic pressure of up to 15 mm Hg. Patients were stratified by pulmonary artery systolic pressure into three grades: 36-50 mm Hg, 50-70 mm Hg and >70 mm Hg [6]. Neonatal complications included: preterm

birth (<37 wk gestation), moderately preterm birth (32-36 wk), very preterm birth (26-31wk), low birth weight (<2500 g), very low birth weight (<1500 g), extremely low birth weight (<1000 g), small for gestational age (below tenth percentile from the mean weight corrected for gestational age and gender, SGA), cardiac birth defects and other birth defects, necrotizing enterocolitis (NEC), intracranial hemorrhage (ICH), and neonatal asphyxia.

*Data analysis*: Data were summarized by descriptive statistics. Data were analyzed using SPSS V. 21. Mean (SD) are presented for normally distributed continuous variables and were compared using Student *t* test. For non-normal continuous variables, Median (IQR) were computed and were compared using Mann-Whitney *U* test. Categorical variables were expressed as proportions and compared using chi-square test or Fisher exact test. Multivariate logistic analysis was utilized to assess the relationship between surgical repair and adverse neonatal outcomes. Two-tailed probability values <0.05 were considered statistically significant.

## RESULTS

Data of 65 pregnant women diagnosed with CHD was included (**Fig.1**); of which, 35 (58.5%) women had simple CHD. In the simple CHD group, cardiac defects were surgically repaired in 12 (31.6%) women. The obstetric characteristics based on complexity of CHD and surgical repair is shown in **Table I**. The neonatal outcomes of women as per the type of CHD and surgical repair are shown in **Table II**.




*CHD: congenital heart disease.*

**Fig. 1** Flow of participants in the study.

Multivariate analysis demonstrated that pregnant women with unrepaired moderate-to-complex CHD had a higher risk of premature delivery [OR (95%CI) 8.4 (1.26-

**Table I Baseline Characteristics of Pregnant Women With Congenital Heart Disease (*N*=65)**

| *Characteristics* | *Simple CHD* | | *Moderate-to-complex CHD* | |
|---|---|---|---|---|
| | *Surgically repaired (n=12)* | *Unrepaired (n=26)* | *Surgically repaired (n=11)* | *Unrepaired (n=16)* |
| Age (y)[a] | 27.7 (3.2) | 28.2 (4.8) | 28.4 (3.5) | 31.5 (7.1) |
| CHD diagnosis | | | | |
| Prior to pregnancy[b] | 11 (91.6) | 10 (38.5) | 11 (100) | 12 (75) |
| During pregnancy | 1 (8.4) | 16 (61.5) | 0 | 4 (25) |
| LVEF (%)[b] | 59.2 (7.5) | 63.5 (5.5) | 67.1 (4.8) | 66.2 (5.6) |
| Oxygen saturation (%)[a] | 98.7 (0.5) | 98.1 (1.9) | 98.5 (0.7) | 94.5 (6.6) |
| PAH (mm Hg) | | | | |
| ≥35-<50 | 2 (16.7) | 6 (23.1) | 0 | 2 (12.5) |
| ≥50-<70 | 1 (8.3) | 4 (15.4) | 0 | 4 (25) |
| ≥70 | 0 | 2 (7.7) | 1 (9.1) | 1 (6.3) |
| NYHA functional class | | | | |
| Class I-II | 11 (91.7) | 21 (80.8) | 11 (100) | 14 (87.5) |
| Class III-IV | 1 (8.3) | 5 (19.2) | 0 | 2 (12.5) |
| Drug exposures | | | | |
| Corticosteroids | 1 (8.3) | 0 | 1 (9.1) | 0 |
| Warfarin[b] | 0 | 0 | 6 (54.5) | 0 |

*Data provided as no (%). [a]mean (SD). [b]P<0.05. CHD-congenital heart disease; LVEF: left ventricular eject fraction; PAH:pulmonary arterial hypertension.*

**Table II Neonatal Outcomes in Pregnant Women With Congenital Heart Disease**

| *Neonatal outcomes* | *Simple CHD* | | *P value* | *Moderate-to-complex CHD* | | *P value* |
|---|---|---|---|---|---|---|
| | *Surgically repaired (n=12)* | *Unrepaired (n=26)* | | *Surgically repaired (n=11)* | *Unrepaired (n=16)* | |
| Gestational age (wk)[a] | 36.6 (2.6) | 36.8 (2.7) | 0.892 | 36.8 (2.1) | 34.3 (2.7) | 0.016 |
| Preterm birth, *wk* <37 wk | 5 (41.7) | 10 (38.5) | 0.851 | 5 (45.5) | 14 (87.5) | 0.013 |
| 32-36 wk | 2 (16.7) | 9 (34.6) | 0.454 | 6 (54.5) | 12 (75) | 0.268 |
| <31 wk | 1 (8.3) | 2 (7.69) | 0.946 | 0 | 2 (12.5) | 0.499 |
| Infant weight (g)[a] | 2812.5 (716.1) | 2831.9 (665.1) | 0.935 | 2720 (645.7) | 2126.8 (711.9) | 0.037 |
| <1000 g | 0 | 0 | — | 0 | 1 (6.3) | 1 |
| <1000-1500 g | 1 (8.3) | 1 (3.8) | 0.538 | 0 | 2 (12.5) | 0.499 |
| <500-2500 g | 4 (33.3) | 9 (34.6) | 0.938 | 4 (36.4) | 13 (81.3) | 0.04 |
| Cesarean delivery | 11 (91.7) | 22 (84.6) | 0.935 | 11 (100) | 15 (93.7) | 1 |
| Small for gestational age | 1 (8.3) | 1 (3.8) | 0.607 | 2 (18.2) | 4 (25) | 0.662 |
| 1-minute APGAR score[a] | 9.3 (1.2) | 9.2 (1.3) | 0.683 | 8.5 (1.3) | 8.1 (1.8) | 0.461 |
| 5-minute APGAR score[a] | 9.5 (1.0) | 9.5 (0.9) | 0.825 | 9.4 (0.7) | 9.4 (0.8) | 0.955 |
| Respiratory distress syndrome | 1 (8.3) | 5 (19.2) | 0.643 | 1 (9.1) | 6 (37.5) | 0.183 |
| Intraventricular hemorrhage | 0 | 5 (19.2) | 0.158 | 3 (27.3) | 5 (31.3) | 0.824 |
| Neonatal asphyxia | 1 (8.3) | 2 (7.69) | 0.946 | 2 (18.2) | 3 (18.6) | 0.97 |
| Necrotizing enterocolitis | 0 | 0 | — | 0 | 1 (6.3) | 1 |
| NICU admission | 3 (25) | 6 (23.1) | 0.897 | 3 (27.3) | 11 (68.8) | 0.034 |
| Length of stay (d)[a] | 13(5-58) | 22.5(17-34.7) | 0.437 | 24(11-26) | 27(14-55.5) | 0.405 |
| Deformity | 0 | 0 | — | 2 (18.2) | 2 (12.5) | 0.683 |
| Recurrence of CHD | 2 (16.7) | 4 (15.4) | 0.92 | 5 (45.5) | 9 (56.2) | 0.581 |
| Neonatal death | 0 | 0 | — | 0 | 0 | — |

*Data provided as [a]mean (SD) or no (%). CHD-congenital heart disease;* NICU-*Neonatal intensive care unit.*

56.07); *P*=0.028], low birth weight [OR (95%CI) 7.58 (1.31-41.92); *P*=0.024], and neonatal intensive care unit (NICU) admission [OR (95%CI) 5.87 (1.08–32); *P*=0.041].

## DISCUSSION

The present study showed that women with simple unrepaired CHD had similar neonatal outcomes as compared to simple repaired CHD. In contrast, neonatal outcomes were adverse in women with moderate-to-complex CHD with unrepaired lesions than the repaired group.

Women with CHD experience longer life expectancy and improved general health with diagnostic and therapeutic advances in recent years. Consequently, more and more women with CHD are reaching reproductive age and are considering pregnancy. CHD increases the incidence of neonatal complications such as premature delivery and SGA, in women without surgical repair of shunt lesions [7]. A few women with CHD were unaware of their heart defects before pregnancy and had not received any surgical repair but tolerated pregnancy and labor well.

Women with an ASD were at an increased risk of SGA and fetal mortality in comparison to women with a repaired ASD in an earlier study [8]. Another study [9] showed that women with repaired VSD had a higher risk of premature labor and SGA births in comparison to women with unrepaired VSD. However, mechanism of a higher risk of neonatal events in women with repaired VSD are not clearly understood. The present study reported a higher risk of premature delivery, low birth weight and NICU admission in women with unrepaired compared with repaired moderate-to-complex CHD. The hemodynamic changes in operated women with moderate-to-complex CHD are well tolerated and appear to be stable during pregnancy. The risks of obstetric complications including hypoxemia, heart failure, arrhythmia and pre-eclampsia, and the risk of fetal and neonatal complications including preterm birth and growth retardation were reported to decrease [10]. Other studies [11,12] have likewise shown improvement in maternal, perinatal and neonatal outcomes. Therefore, cardiac surgery could improve neonatal outcomes and should be performed before conception in CHD.

**WHAT THIS STUDY ADDS?**

- Pregnant women operated for complex congenital heart disease have improved neonatal outcome than women who were not operated.

Other risk factors such as maternal PIH, APH, pre-eclampsia, connective tissue disease and other systematic diseases were reported with adverse neonatal outcomes [13-15]. The numbers of women with CHD and associated comorbidity was very small in this study and were not included for analysis. The present study was also limited by the small sample size and retrospective design.

To conclude, the decision for corrective cardiac repair should be individualized before pregnancy by weighing the risks and benefits. For women with simple CHD, surgical repair before pregnancy does not significantly affect neonatal outcomes, unlike for women with moderate-to-complex CHD, where surgical repair before pregnancy minimizes the risks of neonatal complications.

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RESEARCH PAPER

# Pattern of Psychiatric Emergencies in Children and Adolescents at a Tertiary Care Centre After Onset of COVID-19 Pandemic

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**Objective:** To assess changes in profile of psychiatric emergencies in children and adolescents (aged <19 year) during the coronavirus disease 2019 (COVID-19) pandemic compared to pre-pandemic period. **Methods**: The psychiatric emergency records were analyzed for the period of April, 2019 – September, 2021 to assess the pattern and profile of mental health emergencies in children and adolescents in the period before and after the onset of the pandemic lockdown (i.e., 23 March, 2020). **Results**: 379 consecutive child and adolescent psychiatric emergencies were identified, of which 219 were seen after the onset of pandemic. Commonest reason for referral in the pandemic group was attempted self-harm (44.3%). The ICD-10 neurotic, stress-related and somatoform disorders constituted the commonest diagnostic category, similar to pre-pandemic period. A significantly higher proportion (44% vs 28%) of children was prescribed benzodiazepines in the pandemic period, compared to the pre-pandemic period. **Conclusion**: The average monthly psychiatric emergencies in children and adolescents showed no increase during the pandemic period. Self-harm was the commonest cause of psychiatric referral in emergency services mental health crisis in the younger population.

**Keywords:** *Benzodiazepine, Child and adolescent psychiatry, Mental health*.

International literature indicates that there was a 26% to 60% reduction in emergency visits immediately after the pandemic, especially during confinement periods [1-4]. Studies on mental health emergencies during the peak pandemic months also demonstrated some decline in numbers of psychiatric emergency visits, though that was proportionate to decline in overall emergency department visits. However, the pattern and profile of mental health issues showed some changes in the pandemic period. Some studies reported more suicidal attempts or substance overdoses, while others found an increase of anxiety, stress- related or neurotic presentations [5-10].

Literature on child and adolescent psychiatric emergencies is rather limited and somewhat conflicting. Only one prior Indian study is available on psychiatric emergency department visits after COVID-19 pandemic; however, most of the subjects were adults with no specific focus on younger age group [16]. The study found that there was an overall decrease in total number of all-age emergency visits. In terms of diagnostic distribution, there was an increase in patients for schizophrenia and reduced representation of delirium, while visits with self harm continued at similar rates in pre and post lockdown period.

In view of paucity of reports from India on child and adolescent mental health emergencies with respect to COVID-19 pandemic, we aimed to assess the pattern and profile of psychiatric emergencies in younger age groups after onset of COVID-19 pandemic with respect to pre-pandemic period, and explore for relationship, if any, with month-wise COVID-19 statistics in the country.

## METHODS

A retrospective review of psychiatric emergency records was carried out at Department of Psychiatry, All India Institute of Medical Sciences (AIIMS), New Delhi for the period between April, 2019 and September, 2021. Institute Ethics Clearance was taken prior to study initiation.

The department maintains record of all individuals visiting the emergency department and attended by psychiatry emergency team. After a psychiatric evaluation of the patient, a plan is formulated, and treatment is prescribed. Accordingly, patient is thereafter discharged or kept for observation (usually up to 24 hours), or admitted in the ward, if warranted.

Consecutive child and adolescent patients [17], belonging to either gender, registered in the emergency department of the Institute, and attended by the on-call

psychiatry emergency referral team during the study period were included for the study. Unclear or incomplete case records or those with missing data were excluded. Available demographic and clinical data, including diagnosis, comorbidities, referrals to other specialities, and treatment advice was noted.

*Statistical analysis*: Statistical analysis was done using SPSS 20.0. Descriptive analysis was done for socio-demographic and clinical variables. Study groups prior and after onset of pandemic i.e., March 23, 2020, were compared using chi-square and independent samples t-test.

## RESULTS

A total of 379 child and adolescent patient (160 in pre-pandemic period) records were analyzed, which constituted 16.7% of all-age psychiatric emergencies attendance in that period. The mean (SD) monthly child and adolescent psychiatric emergency referrals in pandemic period was 6.6 (3.1), comparable to pre-pandemic period [6.3 (3.9); *P*=0.798].

**Table I** shows the socio-demographic and clinical variables in pre-pandemic and pandemic groups. Both groups were comparable with respect to demographic variables. Nearly half of them had medico legal presentations. The commonest reason for referral was assessment for self-harm (46% vs 44%) in both groups. Compared to pre-pandemic group, the pandemic group had significantly lower proportion with medical/neurological/

**Table I Characteristics of Children with Referrals for Psychiatric Emergencies During the Pre-pandemic and Pandemic Periods (*N* =379)**

| *Characteristics* | *Pre-pandemic period, n=160* | *Pandemic period, n=219* | *Mean difference (SD)/ OR (P value)* |
|---|---|---|---|
| Age[a] | 16.5 (2.5) | 16.4 (2.5) | 0.22 (0.8) |
| Male gender | 86 (53.8) | 124 (56.6) | 0.308 (0.58) |
| Unmarried[b] | 156 (97.5) | 210 (95.9) | 0.723 (0.57) |
| Medico-legal cases | 76 (47.5) | 108 (49.3) | 0.122 (0.73) |
| Carry-over cases from previous day | 10 (6.3) | 18 (8.2) | 0.524 (0.47) |
| Past medical history | | | 2.024 (0.57) |
| Medical | 8 (5) | 13 (5.9) | |
| Neurological | 15 (9.4) | 16 (7.3) | |
| Surgical | 7 (4.4) | 5 (2.3) | |
| None | 130 (81.3) | 185 (84.5) | |
| Past psychiatric history | 32 (20) | 54 (24.7) | 1.143 (0.28) |
| Medication/s before presentation | | | |
| Psychotropic | 35 (21.9) | 58 (26.5) | 1.486 (0.48) |
| Other medication | 12 (7.5) | 12 (5.5) | |
| None | 113 (70.6) | 149 (68) | |
| Reasons for referral | | | 2.114 (0.78) |
| Self-harm | 74 (46.3) | 97 (44.3) | |
| Neglect | 2 (1.3) | 3 (1.4) | |
| Harm to others | 16 (10) | 30 (13.7) | |
| Diagnostic clarification | 67 (41.9) | 86 (39.3) | |
| Psychiatric clearance | 0 (0) | 1 (0.5) | |
| Others | 1 (0.6) | 2 (0.9) | |
| Precipitating factor | | | 3.921(0.14) |
| Biological | 24 (15) | 24 (11) | |
| Psychosocial | 42 (26.3) | 77 (35.2) | |
| None apparent | 94 (58.8) | 118 (53.9) | |
| Comorbid medical diagnosis in emergency visit[b] | | | 18.282 (<0.001) |
| Medical | 23 (14.4) | 12 (5.5) | |
| Neurological | 22 (13.8) | 13 (5.9) | |
| Surgical | 3 (1) | 2 (0.9) | |
| None | 112 (70) | 192 (87) | |

*All values are in frequency (%) except [a]mean (SD). [b]P<0.01.*

surgical diagnosis during emergency evaluation. On the other hand, while 88% has no known medical diagnosis in the pandemic group, same was 70% in pre pandemic group.

After onset of pandemic, the most common diagnostic category was neurotic, stress-related and somatoform disorders (16.4%), followed by intentional self-harm with no discernible psychiatric diagnosis (15.1%). There were; however, no statistically significant differences between the groups with respect to ICD-10 diagnostic categories. Use of antidepressants, antipsychotics and other psychotropic medications was equally prevalent. However, prescription of benzodiazepines significantly increased in the pandemic group ($P$=0.01; 42% vs 29%) compared to pre-pandemic group. About 9% of children and adolescents attended in the pandemic period were advised psychiatric admission, compared to 15% in pre pandemic group ($P$<0.05%). Only 3.7% got admitted due to various reasons such as unwillingness/refusal, logistic difficulty, or non-availability of beds.

## DISCUSSION

The study adds to the findings from limited literature on child and adolescent psychiatric emergencies, specifically with respect to COVID pandemic in India. The child and adolescent psychiatric emergencies had a clinical prevalence of 16.7% among all-age psychiatric emergencies attended at our center. The monthly average of child and adolescent psychiatric emergency referrals in pandemic period was 6.6 (3.1). Overall monthly service utilization in the pandemic period remained comparable to pre-pandemic group. There was, however, a short-term decline in months coinciding with phases of active lockdown in the city with limited transport facilities, consistent with available literature [10,12-15]. In the context of COVID-19, travel and visits to hospital casualties were avoided to the extent possible due to fears of contracting infection in crowded places. In spite of ongoing pandemic, the monthly average of child and adolescent psychiatric referrals in the pandemic period has remained comparable to the year prior to pandemic, which points to ongoing mental health service needs for younger patient population.

McAndrew and colleagues reported [11] decline in all-age psychiatric emergency visits but found an increase of visits by those less than 18 years. In a large retros-pective study of emergency presentations in children <18 years of age, across ten countries, a reduction in psychiatric

**Table II Characteristics of Children With Referrals for Psychiatric Emergencies in the Pre-pandemic and Pandemic Periods ($N$ =379)**

| *Diagnosis/management* | *Pre-pandemic, n=160* | *Pandemic, n=219* | *Mean difference (SD)/ OR (P value)* |
|---|---|---|---|
| ICD F00-09 | 14 (8.8) | 21 (9.6) | 0.078 (0.78) |
| ICD F10-19 | 10 (6.3) | 14 (6.4) | 0.003 (0.96) |
| ICD F20-29 | 22 (13.8) | 30 (13.7) | 0 (0.99) |
| ICD F30-39 | 26 (16.3) | 28 (12.8) | 0.908 (0.34) |
| ICD F40-49 | 35 (21.9) | 36 (16.4) | 1.795 (0.18) |
| ICD F60-69 | 8 (5) | 11 (5) | 0 (0.99) |
| ICD F70-99[a] | 2 (1.3) | 8 (3.7) | 2.078 (0.2) |
| ICD X60-84 (without F00-99) | 22 (13.8) | 33 (15.1) | 0.129 (0.72) |
| Adverse effect of medication | 2 (1.3) | 4 (1.8) | 0.197 (1) |
| Diagnosis deferred | 29 (18.1) | 36 (16.4) | 0.185 (0.67) |
| Drugs – antipsychotic | 22 (13.8) | 43 (19.6) | 2.253 (0.13) |
| Drugs – antidepressant | 20 (12.5) | 41 (18.7) | 2.650 (0.1) |
| Drugs – mood stabiliser[a] | 4 (2.5) | 5 (2.3) | 0.019 (1) |
| Drugs – benzodiazepine[a] | 46 (28.8) | 92 (42) | 7.02 (0.01) |
| Other drugs | 11 (6.9) | 17 (7.8) | 0.661 (0.42) |
| Referral made (Any) | 61 (38.1) | 96 (43.8) | 1.243 (0.26) |
| Advised psychiatric admission | 24 (15) | 20 (9.1) | 3.102 (0.08) |
| Admitted under psychiatry | 7 (4.4) | 8 (3.7) | 2.194 (0.33) |
| Referred to psychiatry OPD | 111 (69.4) | 146 (66.7) | 0.311 (0.58) |

*All values in no. (%). ICD-10: International Classification of Diseases, 10th Edition; OPD: outpatient department. [a]P<0.01.*

presentations was found, at least in first two months after lockdown [12]. Leeb, et al. [13] found an initial reduction after lockdown, followed by an increased proportion of younger age group psychiatric emergencies in subsequent months. The study by Davico, et al. [14] found a significant decline in numbers of child and adolescent mental health emergencies after onset of pandemic, but with no significant change in hospitalization or in the prevalence distribution [14]. Cheek, et al. [15] found 47.2% decrease in total presentations compared with year before, with a 35% increase in mental health diagnoses. Ferrando, et al. [10] found a decline in pediatric psychiatric emergency numbers; however, child and adolescent patients had more new onset disorders and more likely to be admitted to inpatient care, but less likely to present with suicide attempts, impulse control disorders and agitation/aggression.

The ICD-10 neurotic, stress-related and somatoform disorders (16.4%) was the most common child/adolescent psychiatric diagnostic category in the pandemic group, followed by ICD-10 schizophrenia and other psychotic disorders (13.7%) and ICD-10 mood disorders (12.8%). No significant differences were; however, observed in frequency of ICD-10 diagnostic category across pre pandemic and pandemic group. This finding may contrast with findings from web-based surveys of community residing adolescents which have indicated a substantial rise in symptoms of depression and anxiety during the COVID-19 outbreak [18]; however, those surveys have used screening instruments without diagnostic confirmation and must be viewed as a measure of psychological distress in younger age groups rather than a psychiatric diagnosis. In contrast, the current study focused only on those with a mental health crisis presenting to emergency and assessed by a trained psychiatrist, rather than community-based adolescent sample.

Nearly 44% of emergency referrals in the pandemic period were due to attempted self-harm in the pandemic group, which was similar to the pre-pandemic sample. Self-harm remained an important mental health crisis in child/adolescent population irrespective of pandemic situation in this study. A prior study by Ferrando, et al., found suicidal ideation to be a presenting symptom in nearly 44%, self-injurious behaviour in 8.8% and suicidal attempts in nearly 5%, latter being less likely in post lockdown sample of that study [10]. Another similar study found that the presentations with self-harm or suicidal ideations remained same in adolescents, though there was a rise of anxiety disorders after COVID-related lockdown [11]. A large scale, retrospective cohort study from 23 hospital emergency departments in ten countries (*N*=2,073 visits) found that the proportion of children and adolescents presenting with self-harm significantly increased from 50% in 2019 to 57% in 2020 but there was no difference in the proportion of those with severe self-harm [12]. In our study too, a little less than half of sample (44.3-46.3%) presented to casualty with self-harm.

About 15% of records reflected only X code for Intentional self-harm, with no assigned psychiatric diagnosis. About 16% had diagnosis deferred as per clinical records, though there may have been mental or behavioural issues at time of emergency evaluation. A provisional diagnosis is usually made to the extent possible, and management initiated accordingly. However, those with unclear presentations or sub-syndromal presentations are subjected to psychological tests and detailed evaluations prior to assigning any psychiatric diagnosis. In view of COVID-19 related mortality, issues pertaining to grief and loss were at the forefront especially during second wave, where younger population with still evolving coping skills are most vulnerable [19]. In the post-pandemic sample, one in three psychiatric emergencies reported a psychosocial precipitant, which was similar to pre-pandemic period, though qualitatively different. The nature of psychosocial precipitants, risk and protective factors were not available in retrospectively assessed records.

Interestingly, it was seen that benzodiazepine prescriptions increased significantly in the pandemic group (42% vs 28.8%), in contrast to the rates of other psychotropic prescriptions which remained unchanged. Benzodiazepines may help in alleviation of milder, sub threshold or non-specific anxiety symptoms, for sleep related problems, or for sub-syndromal psychiatric symptoms, [20,21]. However, such symptoms could lead to psychological distress and can become a matter of clinical attention.

In contrast to a prior study [10], our study showed hospitalization rate of psychiatric emergencies was less than pre-COVID period, which might be to promote management of mental health issues at home. Further, routine admissions were also restricted for few months after onset of pandemic, with institute policy permitting only urgent admissions. Other similar studies on younger age group emergencies have reported either a decline [6,22], or similar rates of hospitalizations before and after onset of pandemic [14].

There was a significant reduction in the proportion of referrals with known medical/surgical diagnosis after pandemic, compared to pre-COVID group. This may be due to decreased referrals for minor psychiatric symptoms, as well as avoidance due to fear of poor prognosis of getting hospitalized with COVID-19 with medical comorbidities [23].

**WHAT THIS STUDY ADDS?**

- Self-harm remains an important mental health crisis in child/adolescent population irrespective of pandemic situation.
- Prescription of benzodiazepine was found to be proportionately higher (44% vs 28.8%) in the pandemic period.

The pandemic has not only led to increased rates of acute stress or adjustment reactions but a wide spectrum of psychiatric diagnosis including anxiety, depression, etc [24]. Social factors played an important role during both waves, however the age groups which were most affected by COVID-19 mortality differed somewhat in successive waves. In the first wave, it was seen that the focus was more on geriatric age groups having pre-existing health conditions who suffered more vulnerabilities in physical and mental health. During that wave, the children and adolescents too were impacted due to closures of schools, playgrounds, parks and other such places of socialization with peers. The perceived benefits for some children such as reduced pressure of scholastic performance were later outranked by reduced opportunities for peer interactions and social skills development [25]. In contrast to the first wave, the second wave (and related lockdown) was more severe with more mortalities, resulting in COVID orphans and emergence of related mental health issues, long term consequences of which are yet to be observed [26]. In addition, anxieties associated with school closures, gap years, entrance examinations, grief or loss of loved ones, escalation of domestic violence or economic constraints within families might have added to stressors for the younger population [27, 28].

However, we need to interpret the findings of study in the light of certain limitations. Findings from a tertiary care center in one region may not be generalizable to other centers. The study being a retrospective chart review, we could not obtain more comprehensive psychosocial parameters during the pandemic, and had about 10-20% missing data for various months. Incomplete records, especially around second wave in May, 2021, were not included in the analysis. Also, the measures for temperament, personality traits and other psychosocial aspects were not documented in records; though, they might have been assessed.

The results of the study imply that though the severity of COVID-19 may not be high in children, but the psychological impact is likely to be high. A significantly increased prescription of benzodiazepines for younger age mental health emergencies is another important concern which should not be overlooked, and efforts should be made to follow-up such patients in order to optimise their treatment. Since the psychological impact is likely to continue for longer, it may be worthwhile to raise awareness and identify ways to monitor the psychological impact of COVID-19 on children and adolescents for timely identification and management.

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RESEARCH PAPER

# Sociodemographic and Clinical Characteristics of Child Sexual Abuse Reported to an Urban Public Hospital in Southern India, 2019-22

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**Objective**: To describe the profile of child sexual abuse (CSA) reported to a tertiary care hospital. **Methods**: A retrospective analysis of CSA reported in children aged below 18 years from January, 2019 to June, 2022. **Results**: Out of the 231 cases of sexual abuse reported, 115 (49.8%) were children below 18 years. Most of the victims were children from 10 to 15 years (37.4%), and there were only two male victims. In 89.6%, the perpetrator was known to the victim. Revictimization was seen in 31%. The reported perpetrators were friends (27%), neighbors (34.8%), strangers (10.4%), or fathers (7.8%). Penetrative abuse was seen in 58.3% of reports. External injuries were seen in 6.96%. Eight victims were pregnant and HIV screening was positive in one victim. **Conclusion**: Early identification of CSA is important to prevent revictimization. Children from all age groups can be victims of CSA. Perpetrators can hail from all walks of life of the children.

**Keywords**: *Penetrative abuse, Revictimization, Sexual assault victim*.

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Child sexual abuse (CSA) is under reported in developing countries, due to cultural factors and social stigma [1]. Though many studies are available in the global literature, very few studies have documented its prevalence in India. In the year 2012, the Government of India formulated 'The Protection of Children from Sexual Offences (POCSO) Act' to more effectively address the rising sexual abuse in children. The Ministry of Women and Child Development, Government of India has established a 'One Stop Centre' (OSC) for assisting survivors of gender violence [2], where comprehensive services are provided under one roof. Children, less than 18 years are treated under the Juvenile Justice Act, 2011, and the POCSO Act, 2012 [1]. In a systematic review of 51 studies from India, the prevalence of CSA varied across the studies from 4 to 48% due to the heterogeneity of samples [3]. The authors reiterated the need for a standardized tool for accurate measurement of CSA and also the need for more research regarding the social and psychological profile of the perpetrators of CSA. This study aims to describe the socio-demographic and clinical characteristics of child sexual abuse, as reported to an urban public hospital.

## METHODS

This retrospective descriptive study was done in a Government Medical College Hospital from January, 2019 to June, 2022. The case records of all the children and adolescents less than 18 years of age, reporting to the study hospital, with a history of sexual abuse during the study period, were studied. The cases of elopements were excluded, as they represent a different social issue that is out of the scope of this study. Institutional ethics committee clearance was obtained. The name and identities of the victims were not disclosed. The guidelines of the Ministry of Women and Child Development, Government of India were used for case definitions and management [1]. A standardized form was prepared to collect the data regarding the epidemiological and clinical characteristics of the abuse.

*Statistical analysis:* Statistical analysis was done using Statistical Package for Social Sciences, Version 25. All categorical data were presented as frequency and percentages. To study the association of perpetrators with place, number and type of abuses, Kruskal-Wallis test was applied. *P* value was considered significant at a 5% level of significance for all comparisons.

## RESULTS

The sociodemographic profile of the victims is presented in **Table I**. During the study period, after excluding 175 cases of elopements, there were 231 reported cases of sexual offenses. Out of these 231 cases, 115 (49.8%) were cases of CSA. Nine children reported to the hospital with a parent or caretaker and 106 children were brought by the police. Most of the victims (37.4%) were in the age group of 10 to 15 years. The youngest victim was a 75-day-old

**Table I Sociodemographic Characteristics of Child Victims and Perpetrators (*N*=115)**

| *Characteristics* | *No. (%)* |
|---|---|
| *Child victims* | |
| Girls | 113 (98.3) |
| Age | |
| 0-5 y | 3 (2.6) |
| 6-10 y | 37 (32.2) |
| 10-15 y | 43 (37.4) |
| 16-18 y | 32 (27.8) |
| Class of study | |
| ≤5th standard | 39 (33.9) |
| 6-10 standard | 49 (42.6) |
| ≥11 standard | 27 (23.5) |
| Rural residence | 85 (73.9) |
| *Perpetrator* | |
| Identity known | 103 (89.6) |
| Age | |
| <18 y | 11 (9.6) |
| 19-30 y | 44 (38.2) |
| 31-60 y | 40 (34.8) |
| >60 y | 8 (7) |
| Not known | 12 (10.4) |
| Rural residence | 80 (69.6) |
| Relationship with victim[a] | |
| Neighbor | 40 (34.8) |
| Friend | 31 (27) |
| Stranger | 12 (10.4) |
| Father | 9 (7.8) |
| Uncle | 5 (4.3) |
| Relative | 4 (3.5) |
| Father's friend | 3 (2.6) |
| Cousin | 3 (2.6) |
| Teacher/caretaker | 3 (2.6) |
| Co-worker | 2 (1.7) |

[a]*one each was stepfather, sibling and classmate.*

infant girl and the perpetrator was her father. Two of the victims were boys. In 89.6%, the perpetrator was known to the victim. The oldest perpetrator was aged 70 years and the victim was a 16-year-old girl.

Clinical details of the CSA (**Table II**) show that in 8.7% of cases, more than one perpetrator was involved. The house of the victim (40%) was the most common occurrence of abuse. Re-victimization with more than one incident of CSA was seen at 31.3%. Penetrative abuse was reported in 58.3% of victims. Alcohol abuse was seen in 4.3% of the perpetrators. The urine pregnancy test was positive in eight victims, HIV screening being positive in one victim, while there were no reports of other sexually transmitted diseases. The HIV-positive victim was a 15-year-old girl, residing in an orphanage, who presented with abdominal pain to the hospital. On examination, she was found to be pregnant at 12 weeks of gestation. On investigation by the police, she was found to have been abused multiple times, and by multiple persons.

A significant number of incidents took place in a neighbor's house, when the perpetrator was a friend (*P* =0.013). When the perpetrator was either father or cousin, the abuse occurred multiple times (*P*=0.005 and 0.007, respectively). When the perpetrator was a friend, penetrative forms of CSA were common (*P*=0.028), and when the perpetrator was a stranger, milder forms of CSA like fondling were common (*P*=0.004).

## DISCUSSION

Child sexual abuse is an under-reported medico-social

**Table II Characteristics of Perpetrators and Victims of Child Sexual Abuse (*N*=115)**

| *Characteristics* | *No. (%)* |
|---|---|
| No. of perpetrators | |
| One | 105 (91.3) |
| More than one | 10 (8.7) |
| Place where abuse occurred | |
| House of victim | 46 (40) |
| House of perpetrator | 11 (9.6) |
| Relative/neighbor's house | 33 (28.7) |
| Outdoor (field/farm/roadside) | 15 (13.1) |
| Hostel | 2 (1.7) |
| Lodge | 2 (1.7) |
| School premises | 5 (4.3) |
| Unknown/multiple places | 1 (0.9) |
| Duration of abuse | |
| Less than 30 d | 99 (86.1) |
| 1-12 mo | 10 (8.7) |
| More than one year | 6 (5.2) |
| Time of reporting the incident | |
| Same day | 51 (44.4) |
| Within 1 wk | 15 (13) |
| After 1 week | 49 (42.6) |
| Nature of abuse | |
| Kissing | 10 (8.7) |
| Fondling | 35 (30.4) |
| Masturbation | 2 (1.7) |
| Vaginal sex | 67 (58.3) |
| Oral sex | 1 (0.9) |
| Alcohol abuse[a] | 5 (4.4) |
| External injuries | 8 (7) |
| Intact hymen | 47 (40.9) |
| HIV positive[b] | 1 (0.9) |
| Positive urine pregnancy test | 8 (7) |

[a]*No history of any other intoxicant/drug abuse in the perpetrator;* [b]*victim. HIV: human immunodeficiency virus.*

**Table III Association Between the Perpetrator and Place of Abuse (*N*=115)**

| *Perpetrator* | *Place of abuse* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *House of victim* | *House of perpetrator* | *Hostel* | *Lodge* | *Outdoor* | *Neighbor's house* | *School* | *Unknown house* | *P value* |
| Classmate, *n*=1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0.001 |
| Co-worker, *n*=2 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0.851 |
| Cousin, *n*=3 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0.989 |
| Father, *n*=9 | 8 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0.111 |
| Father's friend, *n*=3 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0.994 |
| Friend, *n*=31 | 11 | 0 | 1 | 2 | 1 | 15 | 1 | 0 | 0.013 |
| Teacher/ caretaker, *n*=3 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 0.002 |
| Neighbor, *n*=40 | 13 | 1 | 0 | 0 | 3 | 22 | 1 | 0 | 0.109 |
| Relative, *n*=3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.961 |
| Sibling, *n*=1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.988 |
| Stranger, *n*=13 | 0 | 1 | 0 | 0 | 10 | 1 | 0 | 1 | 0.001 |
| Uncle, *n*=5 | 4 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0.001 |
| Stepfather, *n*=1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.988 |
| Total | 46 | 3 | 2 | 2 | 15 | 41 | 5 | 1 | |

*Values in numbers.*

problem. In our study, the prevalence of CSA was 49. 8% of all sexual offences reported over a period of 3.5 years. In a similar recent hospital-based study in Punjab, the prevalence was 60% over a two-year period [4]. There has been considerable heterogeneity in the incidence depending on the sample population [3]. Though many studies have demonstrated an increase in reporting of CSA in recent years, the present study showed a sharp decline in the reports of CSA in the two years 2020 and 2021 due to the prevailing lockdown situation and closure of schools during the COVID-19 pandemic [4].

In the present study, there were only two reported cases of boy victims. The lower prevalence among boys was observed in many other studies, which may be attributed to under-reporting, lack of adequate research, and social denial [5]. Depending on the study setting, there has been a wide variation in peak age groups for CSA [4,6]. About 32.2% of the victims were in the age group of 6 to 10 years and hence the educational programs for children against CSA should ideally be targeted at this age group.

In our study, perpetrator was known to the child victim in majority of cases, similar to that reported in other studies [7-9]. A study done in Imphal [10] reported 53.7% of perpetrators to be boyfriends, which is much higher than this study. The lesser reports of the friends as perpetrators in our study could be attributed to the COVID-19 pandemic and the ensuing closure of schools, and/or regional differences. The low proportion of the father, step-father, or sibling as a perpetrator in our study, was comparable to other studies [4,6]. CSA usually happens in places familiar to the child victim, in contrast to adult incidents. In our study, many of the abuses occurred in the house of the victim and neighbor/relative's house; whereas a previous study [10] reported a higher occurrence of the abuses in the perpetrator's house or a private accommodation like a lodging house.

Re-victimization was seen in 31.3% of reports. The 'child sexual abuse accommodation syndrome' that describes the child's reaction to CSA has five stages: secrecy, helplessness, entrapment and accommodation, delayed and unconvincing disclosure of the abuse, and, retraction of the complaint [11]. If uninterrupted, the syndrome paves the way for further re-victimization. This syndrome reiterates the need for early identification of CSA to prevent further re-victimization. A study by Scoglio, et al. [12] reported that perceived parental care is the only preventive factor against re-victimization. In our study, nearly half the cases were reported after a week; whereas, Lal, et al. [6] found that 12% reported after a month of abuse. The delay in reporting the incident is usually due to stigma, fear, and indecisiveness of the parents. They need sufficient time to reconcile themselves from the incident and brace themselves to report the incident [10].

Penetrative sexual abuse is associated with serious psychological stress and physical problems like sexually transmitted diseases and pregnancy. A previous study [13] reported 37.9% incidence of pregnancies, as compared to

**WHAT THIS STUDY ADDS?**

- Profile of child sexual abuse victims and perpetratons are reported from Salem, Tamil Nadu.

9% in our study. There has been considerable heterogeneity in the incidence depending on the sample population. In all reports of penetrative abuse, the hymen was absent or ruptured. The presence or absence of the hymen alone should not be taken as a criterion for confirmation of sexual abuse [14]. In our study, one victim was found to be HIV reactive. A similar observation was not found in any of the previous studies from India.

Pediatricians are often the first contact for a child victim, and they should always consider the possibility of CSA while treating children. The Indian Child Abuse, Neglect, and Child Labour (ICANCL) group of the Indian Academy of Pediatrics (IAP) have developed guidelines for pediatricians to follow when they come across CSA victims [15]. The limitation of this study is that it is a hospital-based study and may not represent the prevalence in the community.

CSA contributes a substantial proportion of all reported sexual offences in a hospital. Early identification of CSA is important to prevent revictimization. As children from all age groups can be victims of CSA, education for children regarding CSA should start as soon as they are comprehensible.

*Ethics clearance:* Institutional Human Ethics Commitee, Govt. Mohan Kumaramangalm Medical College, Salem; No. GMKMC&H/6103/IEC/2022-PAED 4, dated July 27, 2022.
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RESEARCH PAPER

# Serum Occludin and Zonulin Levels in Children With Attention-Deficit/ Hyperactivity Disorder and Healthy Controls

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**Objective**: To evaluate zonulin and occludin levels, potentially associated with immunological pathways in the gut-brain axis, in children with attention-deficit/hyperactivity disorder (ADHD). **Method**: We examined the association between serum levels of zonulin and occluding, and behavioral/emotional problems in children with ADHD. 40 medication-naïve children meeting Diagnostic and statistical (DSM-5) criteria for ADHD (11 females; mean (SD) age 9.4 (1.6) years) and 39 healthy comparisons (12 females; mean (SD) age 9.3 (1.9) years) were studied. Serum zonulin and occludin levels were measured by (ELISA). **Result:** We found higher mean (SD) serum zonulin levels [37.1 (28.2) vs 8.1 (4.5) ng/mL; *P*<0.001) and occludin levels [2.4 (1.6) vs 0.6 (0.4) ng/mL; *P*<0.001] in the ADHD group compared to control group. Serum zonulin levels had a positive correlation with weight (r=0.452; *P*=0.003) and BMI (r=0.401; *P*=0.01) among children with ADHD. Serum zonulin and occludin levels also had a positive correlation with Conners parent rating scale scores (r=0.58; P<0.001), and Strengths and difficulties questionnaire scores (r=0.49; *P*<0.001). Multiple linear regression analysis revealed that age, sex, weight, conduct problems and oppositional sub-scores were significant predictors of increased serum zonulin levels. **Conclusion:** These data confirm an association between ADHD, and serum zonulin and occludin levels. Pathophysiological and clinical significance of these findings needs to be elucidated.

**Keywords:** *Behavioral symptoms, Brain-intestinal axis, Conduct problems, Conners rating scale.*

***Trial registration:*** ClinicalTrials.gov; NCT05502471.

Attention-deficit/hyperactivity disorder (ADHD) is a pervasive neurodevelopmental disorder, and has a worldwide prevalence of 5.9% [1]. Although, the pathophysiology is still unclear, emerging evidence has drawn attention to the role of inflammation [2]. In recent years, the two-way communication between the brain and the gut (i.e., the gut-brain axis) has become a focus of study across a wide range of psychiatric disorders, including ADHD [3]. Likely reflecting their common embryologic origins, tight junctions are essential components of both brain and gut. Increased leakiness of the blood-brain barrier has been suggested to play a role in the inflammatory process [4]. On the other hand, evidence for the possible role of inflammation in ADHD pathophysiology is also increasing [2].

Tight junctions (TJ) are intercellular multiprotein junctional complexes that control intercellular permeability in epithelium and endothelium [5]. Occludin, which is a major component of TJs, plays a key role in maintaining TJ integrity, stability and regulating paracellular permeability [6]. Serum occludin level has been shown to increase secondary to barrier disassembly [7]. A recent study showed elevated concentrations of occludin, which was positively correlated with zonulin concentrations, in people with multiple sclerosis compared with healthy controls [8]. This finding raises the question of whether occludin mediates the relationship between neuroinflammation and the gut-brain axis. Zonulin (pre-haptoglobulin-2), an endogenous protein synthesized by the intestinal mucosa, has been identified as an important regulator of epithelial permeability of TJs [9]. Increased serum zonulin concentrations have been reported in various psychiatric disorders [10,11], as well as in chronic inflammatory diseases [12], but only two studies have focused on ADHD [13,14].

We sought to measure serum zonulin and occludin levels in two groups: an independent sample of rigorously diagnosed medication-naïve children with ADHD and healthy controls, and examine the association between these proteins and behavioral/emotional problems and symptom severity of ADHD.

## METHODS

This prospective single-center study was conducted in a tertiary care hospital in Eastern Turkey between January, 2021 and June, 2021. All study procedures were approved by the institutional review board of our University. Informed consent was obtained from parents of all participants, and clinical trial registration was done. Two groups were studied viz., children with ADHD and healthy controls. Sample size of at least 38 in each group was calculated based on the difference in zonulin levels reported in a previous study [13] with a power of 80% and alpha of 0.05. The ADHD group consisted of children who applied to the department of child and adolescent psychiatry, and met DSM-5 criteria for ADHD. The healthy controls consisted of children recruited from the pediatric outpatient clinics, who were attending the hospital for routine examination or minor complaints.

Inclusion criteria for the ADHD group were: *i*) newly diagnosed ADHD, *ii*) no prior psychotropic treatment for ADHD or any psychiatric disorder, and *iii*) age 6–12 years. Exclusion criteria were: *i*) accompanying autism spectrum disorder or schizophrenia, *ii*) history suggestive of inflammatory/non-inflammatory, metabolic, or autoimmune disease, *iii*) active gastrointestinal disease (e.g., vomiting, diarrhea, constipation, irritable bowel syndrome), *iv*) any special diet history within the past year, *v*) use of corticosteroids or regular intake of medication in the last 6 months, *vi*) body mass index (BMI) >30 kg/m$^2$, and *vii*) cognitive deficits by developmental history. The healthy controls were recruited after a review by the psychiatrist from the same hospital. The same exclusion criteria were applied for them, along with absence of a psychiatric diagnosis.

The children with ADHD were diagnosed by either of the two child and adolescent psychiatrists who confirmed they met the full criteria for ADHD as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [15].

An objective structured form was utilized to collect data on age, sex, education, medication, illness, family, body mass index (BMI), diet, and gastrointestinal complaints data (e.g., diarrhea, constipation). All children were assessed with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children/ Present and Lifetime Version (K-SADS-PL) administered by a child and adolescent psychiatrist. Parents also provided ratings on Conners Parent Rating Scale-Revised Short form (CPRS-R:S), and Strengths and Difficulties Questionnaire (SDQ). The CPRS-R:S includes 27 items rated on a four-point Likert scale with four subscales, inattention, hyperactivity, oppositional and cognitive problems. Higher scores indicate more severity of problems [16]. The SDQ evaluates socio-emotional and behavioral difficulties in childhood. This scale mainly includes five subgroups (prosocial, hyperactivity, emotional, conduct and peer problems) with 25 items [17].

Venous blood specimens were collected from children in both the study groups before breakfast, after overnight fasting. Serum samples were obtained following centrifugation at 4000 r.p.m. for 15 minutes at +4°C and all samples were stored at -80 ºC until further analysis. Zonulin levels were measured using the commercial kit Human Zonulin ELISA Kit (Elabscience), with sensitivity 0.47 ng/mL, and detection range 0.78-50 ng/mL, both intra-inter coefficients of variation <10%. Occludin levels were measured by Human Occludin ELISA Kit (Elabscience), with sensitivity 0.10 ng/mL, detection range 0.16-10 ng/mL, and both intra-inter coefficients of variation <10%.

*Statistical analysis*: All statistical analyses were conducted using SPPS (Statistical Package for Social Sciences) for Windows 23.0. Normality of zonulin and occludin levels was tested by the Kolmogorov–Smirnov test. Log-transform was constructed for the non-normally distributed variables. Categorical data were compared with chi-square test. For continuous data, appropriate tests were performed depending on normality. Pearson or Spearman correlations were examined as appropriate to evaluate relationships between sociodemographic characteristics, zonulin and occludin levels and scale scores. To determine the optimal cutoff values for serum zonulin and occludin levels, Receiver-operating characteristics (ROC) analysis and the Youden index were performed. Analysis of variance (ANOVA) was performed to examine the preeminent effects of diagnosis (ADHD or control), sex (male, female) and their interaction. Analysis of covariance (ANCOVA) was conducted to calculate adjusted means of zonulin and occludin levels. Age, sex, and BMI were added as covariates. Effect size is specified as partial eta-squared ($\eta^2$; small ≥0.01, moderate ≥0.06, large ≥0.14). A stepwise multiple regression analysis was then conducted to investigate independent factors affecting zonulin and occludin levels. Two-tailed statistical significance was accepted at $P$<0.05.

## RESULTS

A total of 79 children aged 6 to 12 years were enrolled (**Table I**). The ADHD and comparison group did not differ in age, sex, and BMI. Both serum zonulin (**Fig. 1**) and occludin (**Fig. 2**) levels were significantly higher in the ADHD group compared to the control group (both $P$ <0.001). Large effect sizes were observed for both zonulin ($\eta^2$ = 0.424) and occludin ($\eta^2$ = 0.462) group differences.

**Table I Characteristics of the Enrolled Children**

| *Characteristics* | *ADHD group (n=40)* | *Control group (n=39)* |
|---|---|---|
| Age (y) | 9.4 (1.6) | 9.3 (1.9) |
| Male gender | 29 (72.5) | 27 (69.2) |
| Weight (kg) | 35.0 (8.9) | 32.5 (8.8) |
| Height (cm) | 133.3 (23.7) | 133.4 (12.5) |
| BMI (kg/m$^2$) | 18.5 (2.6) | 17.9 (2.6) |
| CPRS-R:S[a] | | |
| Inattention | 23.2 (6.1) | 4.9 (3.4) |
| Hyperactivity | 9.0 (4.8) | 2.1 (1.7) |
| Oppositional | 8.7 (4.4) | 3.2 (2.3) |
| Cognitive problems | 12.4 (3.4) | 2.2 (1.7) |
| Total CPRS-R:S score | 48.1 (14.1) | 11.7 (6.2) |
| SDQ[a] | | |
| Emotional problems | 3.3 (2.6) | 1.6 (1.4) |
| Conduct problems | 2.8 (1.8) | 1.1 (0.9) |
| Hyperactivity/Inattention | 7.3 (1.9) | 1.7 (1.2) |
| Peer relationships problems | 2.5 (1.3) | 1.6 (1.0) |
| Total SDQ score | 15.9 (5.2) | 6.2 (3.2) |
| Prosocial behavior | 7.9 (1.6) | 8.3 (1.6) |

*BMI-Body mass index; CPRS-R:S - Conners' parent rating scale-revised short form; SDQ: strengths and difficulties questionnaire. [a]P<0.05.*

The optimal cutoff value of zonulin level was 12.6 ng/mL, with a sensitivity of 78% and specificity of 90%. AUC was 0.858 (95% CI: 0.77-0.94). The optimal cutoff value of occludin level was 0.92 ng/mL, with a sensitivity of 82% and specificity of 85%. The area under the ROC-curve (AUC) was 0.903 (95% CI: 0.83-0.97). Applying the cutoff value for zonulin (12.6 ng/mL), 32 children (80%) in the ADHD group were above this cutoff, compared to 4 (11.2%) in the healthy controls ($P$<0.001). Applying the cutoff value for occludin (0.92 ng/mL), 33 (82.5%) children in the ADHD group were above this cutoff, compared to 6 (18.2%) in the healthy controls ($P$<0.001). There were no significant differences for either age or sex between groups. Serum zonulin levels were significantly higher in females than males in ADHD group. Sex-by-diagnosis interactions were examined in zonulin and occludin levels. Results of ANOVA revealed a significant sex ($P$=0.01) and diagnosis ($P$<0.001) effect for zonulin. Only the diagnosis ($P$<0.001) effect was found to be significant for occludin. However, there was no significant main effect of sex or a sex-by-diagnosis interaction for zonulin ($h^2$ = 0.024) and occludin ($h^2$ = 0.044) levels. Univariate ANCOVA adjusting for sex, age, and BMI continued to show significant group differences in serum zonulin and occludin.

**Table II Multiple Stepwise Regression Analysis Showing Variables Independently Associated With Changes in Serum Zonulin and Occludin Levels**

| *Variables* | *β* | *SE B* | *P value* |
|---|---|---|---|
| Serum zonulin levels | | | |
| Occludin levels | 4.215 | 1.414 | 0.004 |
| Age | -7.019 | 1.550 | <.001 |
| Sex | 9.784 | 4.189 | 0.022 |
| Weight (kg) | 1.839 | 0.311 | <0.001 |
| Conduct problems[a] | 3.188 | 1.557 | 0.044 |
| Oppositional[b] | 1.604 | 0.642 | 0.015 |
| Peer relationships[a] | -3.233 | 1.620 | 0.05 |
| Serum occludin levels | | | |
| Zonulin levels | 0.019 | 0.006 | 0.003 |
| Cognitive problems[b] | 0.078 | 0.030 | <0.010 |
| Emotional problems[a] | 0.138 | 0.066 | 0.039 |

*For zonulin; Occludin, age, sex, weight, height, BMI; CPRS-R:S and SDQ scores were included in the original model. SE B: standard error of the mean. For occludin; Zonulin, age, sex, weight, height, BMI; CPRS-R:S and SDQ scores were included in the original model. [a]SDQ score; [b]CPRS – R:S score.*

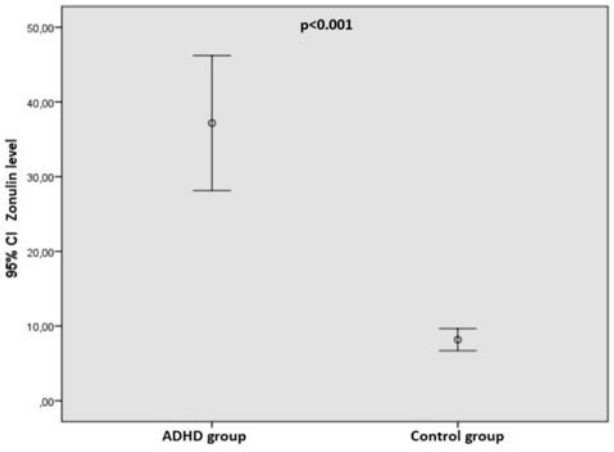


**Fig.1** Serum zonulin levels in the ADHD and the control groups.

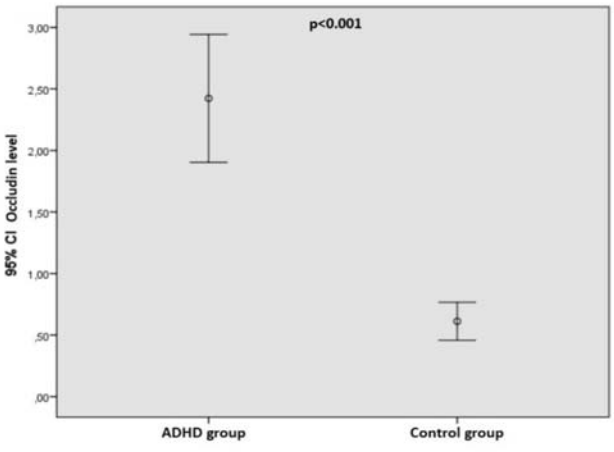


**Fig. 2** Serum occludin levels in the ADHD and the control groups.

Among the children with ADHD, we found statistically significant correlations between zonulin and weight (r= 0.452, *P*=0.003) and zonulin and BMI (r=0.401, *P*=0.01). No significant correlations were found between occludin levels and these parameters. Across all children, all CPRS-R:S sub-scores and some of the SDQ scores (conduct problems, hyperactivity/inattention and total score) were significantly correlated with zonulin and occludin levels (**Web Table I**). However, none of these correlations remained significant within the ADHD group (*P*>0.05). Also, zonulin and occludin levels were not related to ADHD presentation types or ADHD severity in children with ADHD (*P*>0.05).

Finally, across the entire sample, zonulin and occludin levels were significantly and positive correlated (r = 0.565, *P* <0.001). Aiming to control potential confounding variables and identify which parameters are significantly associated with zonulin in the whole sample, we selected age, sex, weight, height, BMI, occludin and all CPRS-R:S, and SDQ scale scores as independent variables and serum zonulin as a dependent variable in multiple stepwise regression analysis (**Table II**). A multiple stepwise regression analysis was conducted with the same independent variables and zonulin for serum occludin levels (**Table II**).

## DISCUSSION

This is the first study to evaluate serum zonulin (a marker and modulator of TJ permeability) and occludin (a regulator of formation, maintenance, and function of TJ) levels in children with ADHD and age/sex-matched healthy comparison subjects. We found increased serum zonulin and occludin levels in the ADHD group compared to health control. In addition, our data shows oppositional and conduct problems to be associated with increased zonulin levels.

The two prior studies on serum zonulin levels in ADHD have produced conflicting results. An initial study found elevated serum zonulin levels in children with ADHD than in health control, which were associated with social dysfunction and ADHD symptom severity [13]. We confirmed increased serum zonulin levels in ADHD group, but in our sample, serum zonulin levels were associated with behavioral/emotional problems.

Our results differ from those of a recent study [14], which failed to find a difference in zonulin but instead found elevation of claudin-5 (a TJ-forming protein functionally similar to occludin). We cannot resolve these inconsistencies, which could be secondary to any of several factors, including differences in analytic kits to quantify levels. Our findings are consistent with a meta-analysis that shown an association between increased plasma zonulin level and impaired intestinal barrier function in children with a range of neurodevelopmental disorders [18]. We conclude that further studies of zonulin in ADHD and neurodevelopmental disorders are warranted, with greater focus on quantifying gastro-intestinal function in addition to standard behavioral ratings.

The number of studies investigating the sex differences in zonulin and occludin levels is limited. In affective disorders, serum zonulin was found to be significantly higher in women than in men, suggesting that increased serum zonulin levels may represent a particularly heightened sensibility for depression [11]. In our study, zonulin levels were considerably higher in females than males in ADHD group; although, none of the sex by diagnosis interactions reached significance. This suggests that there may be a sex difference in children with ADHD in terms of zonulin levels. The number of females included in our study was relatively low. This issue can be re-analyzed in future studies, especially by paying attention to the homogeneity of the distribution of the males and females.

Importantly, weight and BMI showed a significant positive correlation with serum zonulin levels among ADHD group, conforming to previous studies [10,14] showing a positive correlation with BMI. Moreover, increased serum zonulin levels have been reported in obese children compared to healthy children [19], therefore obesity was an exclusion criterion in our study. Despite this, serum zonulin levels showed a significant positive association with weight and BMI.

This study has some limitations, including a relatively small sample size and cross-section design. The most important limitation is that our convenience control sample differed from the ADHD sample in socio-economic status. The mentioned factors limit the generalizability of our findings.

In conclusion, we found significantly higher serum zonulin and occludin levels in children with ADHD than in sex- and age-matched healthy controls. Independent replication of these preliminary results would motivate further examination of intestinal permeability and possibly other components of TJs in the gut and/or brain. Future research should focus on alterations in serum zonulin and occludin levels in diverse ADHD subgroups (for example, after symptoms have been controlled with medication). In addition, further studies comparing ADHD subgroups enriched for oppositional defiant disorder and conduct disorder should be a priority.

**WHAT THIS STUDY ADDS?**

- Serum zonulin and occludin levels were significantly higher in children with attention-deficit hyperactivity disorder (ADHD) group compared to healthy controls.

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**Web Table I Correlation between CPRS-R:S and SDQ Scores and Zonulin and Occludin Levels (*N*=79)**

| *Scales/subscales* | *Correlation coefficient (r)* | |
|---|---|---|
| | *Zonulin* | *Occludin* |
| *CPRS-R:S* | | |
| Inattention | 0.471[a] | 0.562[a] |
| Hyperactivity | 0.290[b] | 0.479[a] |
| Oppositional | 0.413[a] | 0.493[a] |
| Cognitive problems | 0.492[a] | 0.*568*[a] |
| Total CPRS-R:S score | 0.479[a] | 0.584[a] |
| *SDQ* | | |
| Emotional problems | 0.012 | 0.259[c] |
| Conduct problems | 0.256[c] | 0.302[a] |
| Hyperactivity/inattention | 0.455[a] | 0.541[a] |
| Peer relationships problems | 0.076 | 0.102 |
| Total SDQ score | 0.363[a] | 0.498[a] |
| *Prosocial behaviour* | 0.024 | 0.113 |

*CPRS-R:S - Conners parent rating scale-revised short form; SDQ - Strengths and difficulties questionnaire. Spearman correlation coefficient.* [a]*P<0.001;* [b]*P<0.01;* [c]*P<0.05.*

# Genetic Counselling for Global Developmental Delay/Intellectual Disability (GDD/ID) - Changing Landscapes and Persisting Challenges

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Challenges in counselling the family of a child with mental retardation (sic) were highlighted by Dr. Seeta Sinclair in the February, 1973 issue of *Indian Pediatrics* [1]. The article stresses on the need for a family centric approach, focusing not only on improving the capabilities of a child with mental retardation but also attempting to resolve the issues in a holistic manner. It also conveys the importance of understanding comorbidities that accompany these children, and address them simultaneously for improvement in outcomes. Counselling of an index case with global developmental delay (GDD), currently the preferred term for children aged 5 years or intellectual disability (ID) for children who have attained the age of 5 years, still remains a difficult arena for the physician, the genetic counsellor, and the social worker.


## THE PAST

Counselling is an American term coined by Carl Rogers, who lacking a medical qualification, was prevented from calling his work psychotherapy [2]. The concept of this important specialty started after the World War II. In its evolution the term stems back to its initial use in tribal population and in essence can be traced back to the thoughts and dreams discussed in a common session of a meeting with senior members of the tribe. It subsequently shifted with modernization, to the priests who would listen patiently and advise parsimonies. Counselling was initially imparted to help people navigate difficult situations such as death of loved ones, divorce, natural disease, birth of a child with disability amongst other causes. The basic premise of counselling still remains the same as it intends to direct life situations in the correct perspective, approach challenges and find feasible and practical solutions.

The article [1] focusses on parental counselling with specific reference to a child with mental retardation. Using the correct terminology, utilizing changes in age-appropriate nomenclature has been emphasized in the article. The stress on utilization of appropriate tests to comprehend the level of intellect has been delved in adequately. Confounding factors like stressors, familiarity with tests and the reduction in fear of the tests being administered are discussed to change the interpretation of the tests leading to overscoring in performance [1]. Crnic, et al. [3] also reiterate the inconsistencies in the interpretation of tests due to methodological issues, which focus on unidimensional variables with unimodal measurements.

Discussion on transmission of diagnosis in the presence of both the parents is stressed upon, without alluding to genetic counselling. Concepts including guilt, blame, disagreement and mutual discomfort of not revealing certain issues between both parents are detailed. The knowledge of differential behavior adaptation of both parents has been a major aspect in discussion related to the differentially abled child. The difference in the management of such an ordeal and later an adaptational or transformational journey that they embark is worth pondering upon [4]. It is even more important to eliminate the concept of guilt, which accompanies this revelation. The authors remark that it may be futile to discuss the fact if one parent is responsible for the genetic transmission, as it serves no useful purpose [1]. In the era of internet, it may not be possible to conceal this piece of information. Nonetheless, counselling in X-linked and mitochondrial disorders is still a challenge, even to an educated, computer savvy family. Thus, there is a paradigm shift on divulging the diagnosis and mode of transmission to assure that the subsequent trauma can be avoided with medical termination of pregnancy, if the family so desires

after a concrete diagnosis is made and mode of inheritance in the index case can be established.

The authors [1] address the need for multidisciplinary health care assessments needed for holistic evaluation of a child with GDD/ID. Establishing a firm diagnosis is important before it is divulged to parents. The author has also brought to attention that simultaneous addressal of deficits in speech, vision, hearing, management of spasticity are likely to improve outcome in a holistic manner [1]. The basic tests for evaluating a child with GDD/ID include those easily available like radiological evaluation, urinary examination for inborn errors of metabolism and karyotype for those with a suggestive facial gestalt. Radiological evaluation, basic urinary metabolites testing, and karyotyping on an individualized basis were advised in the article along with delineation of dysmorphic features, if any. A skeletal survey is still useful for evaluating skeletal dysplasias and storage disorders where characteristic changes can be appreciated. Pharmacotherapy for hyperactivity and aggression are also elaborated upon. Though not mentioned as autism spectrum disorder (ASD), the use of specific medication has been outlined [1].

## THE PRESENT

Scientific and technologic discoveries are constantly transforming our understanding of genetic and genomic disorders including GDD/ID/ASD. Though, the social and emotional stigma persists and the rehabilitative aspects of these neurodevelopmental disorders are still in evolving stage, there has been significant and expanding comprehension of the molecular etiology, and availability of multitude of genetic, neurometabolic, and neuroimaging investigations. Genetic counselling related to management, prognosis and recurrence risk has also undergone significant change. The cost of these genetic testing maybe forbidding in today's date for the general public. However, as the testing evolves and becomes easily available, the price of the tests is likely to decline significantly. Thus, providing a genetic diagnosis to majority of patients with suspected genetic etiology for GDD/ID/ASD, will soon become a reality.

An exhaustive clinical evaluation including pedigree charting, review of the antenatal and developmental history, and deep phenotyping, still forms the foundation of accurate diagnosis and likely successful outcome of genetic testing. Easy accessibility of many online databases related to human genes and genetic phenotypes have refined clinical approach. With the advent of computer-learning algorithm in clinical medicine, availability of artificial intelligence (AI) software like "Face2Gene" has become a handy tool to the clinician for enhancing their differential diagnosis and in improving genomic data interpretation. Face2Gene (F2G, FDNA Inc, *https://www.face2gene.com/*) is a smart-phone based computerized facial dysmorphology analysis program that analyses 2-dimensional facial images along with clinical characteristics to provide a list of candidate disorders. Others like Online Mendelian Inheritance in man (*https://omim.org/*), ClinVar (*https://www.ncbi.nlm.nih.gov/clinvar/*) are free databases that can also be relied upon.

An underlying genetic etiology contributes to up to 50 % of cases of GDD/ID [5]. The most recent published guidelines on genetic evaluation of GDD/ID and ASD by the American Academy of Pediatrics (AAP) [6] and the American College of Medical Genetics and Genomics (ACMG) [7] respectively, unanimously recommend a tiered approach to genetic testing. A similar stratified approach has also been alluded to in the Indian context [5,8]. A genome wide chromosomal microarray (CMA) testing constitutes the first-tier genetic test for any patient with unexplained GDD, ID, and/or ASD. CMA detects sub-microscopic chromosomal aberrations and has a diagnostic yield up to 10%, and higher (up to 15-20%) in patients with multiple congenital anomalies vis-à-vis karyotype, which has a diagnostic yield of 3% in such cases [9]. CMA has replaced a conventional G-banded karyotype as a first-tier test unless there are evident features of chromosomal aneuploidy (e.g., Down syndrome) or a history of recurrent miscarriages where karyotype still forms the basic test [9,10]. Neuroimaging techniques like magnetic resonance imaging (MRI) to magnetic resonance spectroscopy (MRS) and nuclear magnetic resonance (NMR) are of proven value in unravelling a case with GDD/ID.

Testing for single gene disorders like tuberous sclerosis and Lesch-Nyhan syndrome has become less labor intensive, cheaper and faster with the arrival of next generation sequencing (NGS) technology. NGS is a high throughput sequencing technology enabling simultaneous sequencing of multiple genes which can be done as a panel of GDD/ID/ASD specific genes or can include whole exome or whole genome sequencing. Various studies have reported a high diagnostic yield of whole exome sequencing (WES) up to 40% in patients with ID [11-13], especially if a trio sample (proband and parents) is tested. With further advancement of exome sequencing technology in combination with robust bioinformatic pipeline for assessment of copy number variations, WES may soon become a dependable first tier analysis in non-specific GGD/ID/ASD. CMA and WES tests being high throughput in nature, may identify variants which may not have strong enough evidence to ascertain their clinical significance. Hence, pre-test and post-test counselling which encompasses the advantages and limitations of these tests is an important facet of genetic counselling in today's era.

Screening for inborn errors of metabolism (IEMs) in individuals with GDD/ID/ASD has also witnessed a significant technological advancement like tandem mass spectrometry (TMS) and gas chromatography mass spectrometry (GC-MS) to screen for amino acid metabolism disorders, fatty acid oxidation defects and organic acidurias. Neurometabolic diseases account for 10% of cases of GDD/ID [14] and this etiological group has a potential for complete or near complete modification of phenotype. Apart from dietary supplementation of the deficient metabolite like pyridoxine or pyridoxal phosphate for pyridoxine responsive epilepsy and creatine in creatine transporter deficiency, there has been advancement in availability of metabolic-disease specific formulas like isoleucine, leucine and valine free diet in maple syrup urinary disease and phenylalanine and tyrosine poor diets and drugs like nitisinone in tyrosinemia 1. The ease of import regulations since 2017, by the country's regulatory authority – FSSAI (Food Safety and Standards Authority of India) under the Diet4Life initiative, has made the import of these critical medical foods simpler and faster. Lysosomal storage disorders like mucopolysaccharidoses types I and II, are another group of disorders associated with GDD/ID, which have become amenable to treatment by enzyme replacement therapy (ERT). Currently, cost of ERT is prohibitory and is mainly accessed through charitable initiatives of manufacturers and clinical trials or are occasionally provided to affected children of employees of some central and state government organizations, which bear the cost of treatment.

Discussion about risk of recurrence and appraisal about the reproductive choices to the couple in subsequent pregnancies forms an integral part of the counselling process. Various available options are prenatal diagnosis by means of chorionic villus sampling or amniocentesis and in vitro fertilization (IVF) with pre-implantation genetic diagnosis. For disorders with mitochondrial inheritance, there is now the option of mitochondrial transfer also known as three-parent IVF, which involves genetic materials of three people i.e., the nuclear DNA of the biological father and mother and the mitochondrial DNA of a healthy egg donor.

Guidance about rehabilitation of children with GDD/ID/ASD is crucial to the counselling session. Current child development clinics and district early intervention centers, apart from offering counselling imparted by the developmental pediatricians themselves, are equipped with a physiotherapist, a medical social worker, a speech therapist, and an occupational therapist. These one stop centers have been created to deliver the best possible outcomes in adaption of the family and the affected child.

An important aspect of genetic counselling is also to provide information about the available resources such as Government support schemes and disease-specific support groups. The Government of India has launched the National Policy for Rare Diseases (NPRD), 2021 for the treatment of rare disease patients (*https://main.mohfw. gov.in/sites/default/files/Final%20NPRD%2C%202021.pdf*).Under this policy, rare diseases have been identified and there is a provision for one-time financial support of up to Rs. 50 lakhs either at one time or in a staggered manner to the patients suffering from any rare disease and for treatment in any of the Centre of Excellence (CoE) mentioned in NPRD-2021, outside the umbrella scheme of Rashtriya Arogaya Nidhi. Initially eight Centres of Excellence (CoEs) were identified for diagnosis, prevention and treatment of rare diseases and this number has increased significantly over a short period of time. Five Nidan Kendras have been set up for genetic testing and counselling services. These Government initiatives have brought a ray of hope for parents with children with neurodevelopmental disorders. By virtue of social media, reaching out to the various disease specific support groups and online resources have become feasible now for the parents. Accurate genetic diagnosis puts an end to the diagnostic odyssey, provides a natural history of the disease, facilitates enrolment in clinical trials and provides basis for prenatal diagnosis.

## THE FUTURE

The inclusion of expanded newborn screening for disorders of amino acid, fatty acid and organic acid metabolism in a mandate or a national law will go a long way in preventing GDD/ID before significant brain damage occurs. Precision medicine in patients with GDD/ID/ASD will soon be possible as the advances in genomic medicine continue. Gene therapy and stem cell therapy will be options available for a significant proportion of disorders. There is hope that the availability of cutting-edge diagnostic tools and multiple curative options will change the dynamics of counselling of the parents and would minimize the mental, social and emotional trauma inherent to dealing with a child with GDD/ID/ASD.

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I, Dr Devendra Mishra, hereby declare that the particulars given above are true to the best of my knowledge and belief.

Sd/ Dr Devendra Mishra
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# Effect of High Sodium Intake (5 mEq/kg/day) in Preterm Newborns (<35 Weeks Gestation) During the Initial 24 Hours of Life: *A Non-Blinded Randomized Clinical Trial*

The objective was to analyze effect of early sodium administration in preterm newborns <35 weeks of gestation. The development of hypo- and hyper-natremia, complications, and mortality showed no difference between high sodium and low sodium groups. The percentage of weight loss from birth to 48 hours (7.13% vs 4.08%) and 72 hours (9.02% vs 6.34%) was significantly lower in the high sodium intake group (*P*=0.036). Early sodium implementation in preterm newborns may improve weight loss and decrease related complications.

**Keywords:** *Complications, Hyponatremia, Weight loss*.

**Trial registration**: ClinicalTrials.gov; NTC 04035564

Electrolyte and fluid management is a challenge in premature newborns; up to 25% infants younger than 33 weeks of gestational age develop serum sodium alterations [1]. Preterm infants are at risk of hyponatremia due to reduced glomerular filtration rate, limited kidney sodium reabsorption, and increased arginine-vasopressin levels in response to illness; this impacts growth, and occurrence of preterm-related compli-cations [1,2]. We investigated the effect of early sodium adminis- tration on preterm newborns, by hypothesizing that early sodium administration might impact growth and sodium imbalance, with no adverse effects.

A randomized clinical trial to analyze the impact of sodium intake was conducted between March, 2018 and April, 2020 at our center. The hospital's Ethics in Research committee approved the protocol, and informed consent was obtained from parents or legal guardians of each patient.

Newborns with less than 35 weeks of gestation and less than 24 hours of life were eligible to participate. Patients with major birth defects such as urinary tract malformations, abdominal wall defects, intestinal atresia or obstruction, and congenital heart defects were excluded. The neonates were randomized using a random number generator with a 1:1 allocation ratio to two groups viz., the control group (sodium intake <1 mEq/kg/day) and the intervention group (sodium intake of 5 mEq/kg/day). There was no blinding done. The dose in the intervention group was selected according to previous publications [3,4]. The sodium delivered was calculated from the sodium concentration and volume of fluid administered, including colloid, crystalloid, drugs, and flush volumes. The percentage of sodium in the fluids administered to each group of patients varied according to the needs of each participant, the solutions were prepared according to the supervision of the investigators involved in this protocol to assure the adequate delivery of sodium per kg according to the group. In average, the intervention group received maintenance fluids consisting of 0.25% sodium, and the control group received maintenance fluids containing 0.02% sodium.

The intervention was initiated at 24 hours of life, ending at 72 hours; all participants received standard care regarding fluid administration in different gestational ages and sicknesses according to clinical practice guidelines. The intervention was discontinued if parents withdrew consent midway, adverse effects attributable to the intervention were detected, or proto-col violation occurred.

The sample size was calculated using a bilateral test to contrast a qualitative endpoint, with a 95% confidence level (1-$\alpha$) and an 80% statistical power; the proportion of patients with the primary endpoint in the control group and the intervention group were selected according to previous publications (50% and 20%, respectively) [2,4,5], resulting in a sample size of 38 patients in each group.

The primary outcome measure was developing hyponatremia or hypernatremia (serum sodium < 130 mEq/L or >150 mEq/L) during the first 72 hours of life. The secondary outcome endpoints were the length of in-hospital stay, mortality, weight and sodium change through time, development of sepsis, necrotizing enterocolitis, intraventricular hemorrhage, and bronchopulmonary dysplasia.

Serum sodium was measured using ion selective electrode in the laboratory. The renal functions were followed by daily assessment of urine output and serum creatinine, and calculation of the glomerular filtration rate. The monitoring of adverse effects was conducted due to close monitoring of clinical and laboratory parameters.

Chi-square test, independent sample *t* test, and risk ratios were used to compare differences between groups. The change in variables with time was evaluated using repeatedmeasures analysis of variance. The intention-to-treat analysis was not conducted as it may underestimate

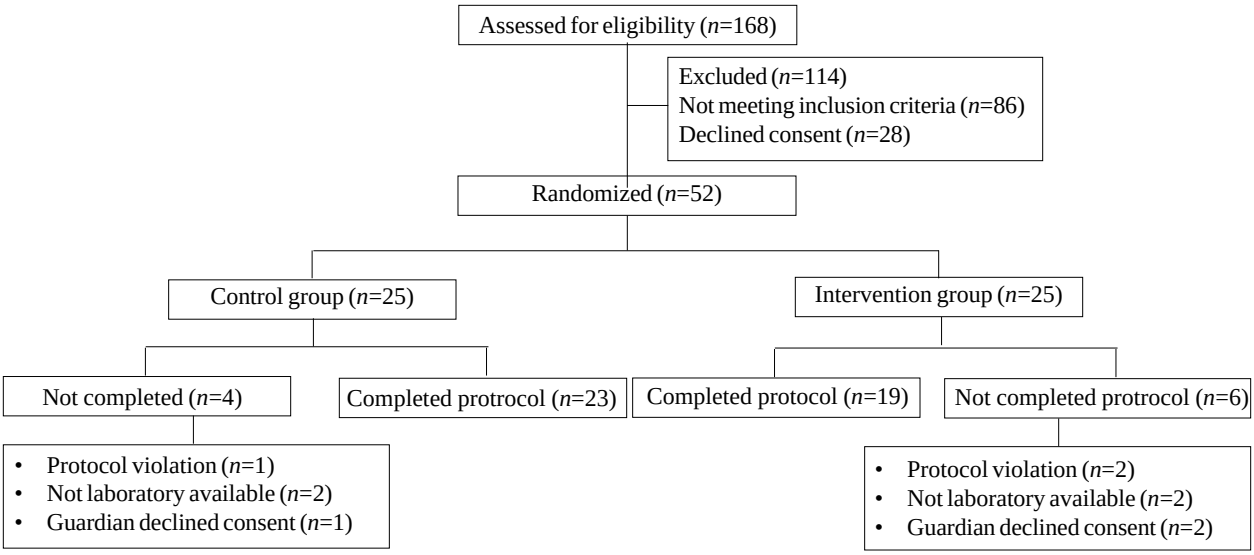


**Fig. 1** Clinical trial flow chart.

the actual intervention effect (type II error) and may create heterogeneity in the sample. A *P* value <0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp).

Of the 52 randomized patients, 42 completed the study. The reason for not completing was protocol violations such as fluid and sodium administration and delayed laboratory samples (*n*=3); no laboratory available (*n*=4); and withdrawal of consent after enrollment (*n*=3). Finally, 23 patients were enrolled in the control group and 19 in the intervention group. Birth weight, sex, and gestational age showed no statistical difference between the groups (**Fig.1**).

The mean (SD) sodium dose in the intervention group was 5.06 mEq/kg/day, and in the control group, 0.41 (0.2) mEq/kg/day.

Mortality was slightly higher in the control group, 21.7%, against 10.5% in the intervention group; however, no statistical significance was demonstrated (*P*=0.33). The length of hospital stay, hypernatremia, and complications related to prematurity showed no difference between the groups. The development of hyponatremia accounted for six patients (26.1%) in the control group against one patient (5.3%) in the intervention group; despite the higher frequency in the control group, (*P* =0.071).

When analyzing the percentage of weight change through time; the difference from birth to 24 hours showed no relevance between groups; nonetheless, the control group from birth to 48 hours presented a mean loss of 7.13% (vs 4.08%) of weight, and from birth to 72 hours, a loss of 9.02% (vs 6.34%) of weight (*P*= 0.036).

There was no increase in complications or adverse effects in our study due to increased sodium intake. The relative risks (95% CI) for hypernatremia [1.21 (0.08, 8.0); *P*=0.88] and hyponatremia [0.20 (0.02, 1.53); *P*=0.12] were not significant (**Table I)**.

Anecdotal publications mention that sodium intake should be delayed until postnatal loss of body water, due to the risk of hypernatremia, fluid retention, and other complications [3]. Nonetheless, it has been demonstrated that sodium deficiency in preterm infants is a risk factor for complications: Al-Dahhan, et al. [6] concluded that sodium intake in premature infants might be optimized in the first days of life to prevent side effects of hypo-natremia in growth and nervous system development. Other studies demonstrate that early sodium intake does not increase the frequency of complications and may be beneficial to preterm newborns [4,7]. Vanpée, et al. [7] demonstrated that sodium supplementation in preterm newborns improved weight gain and stabilized serum sodium value. Similarly, when studying preterm new-borns, Isemann, et al. [5] reported improvement in growth and a decrease in the development of hyponatremia. In our study, the weight gain improved in the sodium-supplemented group, but we did not find a statistically significant impact on hyponatremia; however, we started sodium intake earlier than in the studies mentioned above.

It is recommended to prescribe sodium to newborns after weight loss has been achieved; although, some

**Table I Characteristics and Outcomes of Preterm Newborns (*N*=42)**

| | *Control group (n=23)* | *Intervention group (n=19)* | *P value* |
|---|---|---|---|
| Female | 12 (52.2) | 8 (42.1) | 0.51 |
| Birth weight (g)[a] | 1551 (447) | 1609 (394) | 0.66 |
| Gestational age (wk)[a] | 32 (2.0) | 32.05 (2.4) | 0.94 |
| Hypernatremia | 1 (4.3) | 1 (5.3) | 0.89 |
| Hyponatremia | 6 (26.1) | 1 (5.3) | 0.071 |
| IVH | 6 (26.1) | 4 (21.1) | 0.70 |
| BPD | 1 (4.3) | 2 (10.5) | 0.43 |
| NEC | 2 (8.7) | 2 (10.5) | 0.84 |
| Sepsis | 8 (34.8) | 5 (26.3) | 0.55 |
| Mortality | 5 (21.7) | 2 (10.5) | 0.33 |
| Hospital stay (d)[a] | 28.4 (16.2) | 24 (18.3) | 0.49 |
| *Weight change*[c] | | | |
| 24 h[b] | -1.003 (0.54) | -2.67 (0.8) | 0.12 |
| 48 h[b] | -7.13 (0.79) | -4.08 (0.75) | 0.036 |
| 72 h[b] | -9.02 (0.97) | -6.34 (0.90) | 0.036 |
| *Serum sodium change*[d] | | | |
| 48 h[b] | 3.18 (1.75) | 5.94 (1.93) | 0.29 |
| 72 h[b] | 1.92 (1.54) | 5.71 (1.70) | 0.10 |

*Data presented as no. (%), [a]mean (SD) or [b]mean (standard error). IVH-intraventricular hemorrhage; BPD-bronchopulmonary dysplasia; NEC-necrotizing enterocolitis. [c]Compared to birth weight. [d]Compared to serum sodium at 24 h of life.*

authors have recommended sodium intake in preterm infants ranging from 1 to 3 mEq/kg/day during the first three days of life, this may be insufficient to maintain an adequate sodium balance [2,8]. Despite this, there is a lack of consensus on whether or not and when to prescribe sodium supplementation in preterm newborns. Segar, et al. [9] stated that a targeted approach that identifies sodium deficiency in premature infants and guides sodium intake might be preferable [9]. Currently, study protocols are being developed to answer this unresolved question [10]. However, there is a limited number of publications about this issue.

In conclusion, early sodium implementation in preterm newborns may be beneficial and safe; it may improve weight and decrease related complications. This study has limitations, such as a small sample size, the variability of the sodium concen-tration in fluids, and the few reports of the literature to contrast with. Therefore, further updated studies are needed to implement an adequate recommendation regarding the dose and initiation of sodium supplementation.

*Ethics clearance*: The study was approved by the Ethics in Research Committee of Hospital del Niño "Dr. Federico Gomez Santos" approved the protocol (01/03/18N01) and was registered at *clinicaltrials.gov* (NTC04035564). The study was performed according to the Declaration of Helsinki. Informed consent was obtained from all parents or legal guardians of each patient.

*Contributors*: CS,DC,VDB,FC: contributed to the conception and design of the research, collection, and analysis of data, revision, and approval of the manuscript. Authors declare responsibility for the entire manuscript.

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# Successful Management of Systemic Pseudohypoaldosteronism Type 1 in an Infant

Pseudohypoaldosteronism (PHA) type 1 is characterized by end organ resistance to the action of mineralocorticoids and manifests as neonatal salt wasting [1]. The autosomal dominant and less severe form, also known as renal PHA type 1 (PHA 1a) is caused by mutation in mineralocorticoid receptor (MR) in the kidney, with isolated renal salt wasting. Mutations in any of the three subunits (alpha, beta or gamma) of the epithelial sodium channel (ENaC) results in the autosomal recessive systemic PHA type 1 (PHA 1b). This form is characterized by sodium wasting in the kidneys, lungs, colon, sweat and saliva. In contrast to the renal form, patients have recurrent respiratory infections and a more severe disease that requires lifelong therapy [2,3]. PHA type 2 (Gordon syndrome) is a rare renal tubular defect that results from mutation in *WNK*1 or 4, and is characterized by hypertension and hyperkalemic metabolic acidosis in the presence of low renin and aldosterone levels. Herein, we report a neonate with systemic PHA type 1 who was managed successfully despite a tumultuous course.

An 18-day-old baby boy was under treatment for poor weight gain, electrolyte imbalance, metabolic acidosis and sepsis. The baby was born as late preterm through non-consanguineous marriage with a birth weight of 2.5 kg and an uneventful perinatal period. He was symptomatic since day 8 of life in the form of lethargy and poor feeding. There was no history of fever, cough, respiratory distress, vomiting, loose stools, skin lesions, seizures or decreased urine output. He was managed with intravenous fluids and antibiotics, and potassium lowering measures (calcium gluconate, potassium binding resin and insulin infusion). The baby was resuscitated after an episode of cardiac arrest on day 10 of life due to severe hyperkalemia (11.6 mEq/L). Peritoneal dialysis was initiated and continued for 7 days in view of persistent hyperkalemia. He was started on hydrocortisone and fludrocortisone for suspected classical congenital adrenal hyperplasia (CAH). He was then referred to us for further management.

At presentation, he was sick looking, lethargic and had dehydration and acidotic breathing. His weight was 2.3 kg, length 52 cm and head circumference 34 cm. Genitalia was normal male phenotype and there was no hyperpigmentation. The differential diagnosis considered were late-onset neonatal sepsis, CAH with adrenal crisis, aldosterone synthase deficiency, congenital adrenal hypoplasia, and PHA. Laboratory evaluation showed metabolic acidosis, sodium 114 mEq/L, potassium 6.5 mEq/L and normal renal function tests. Blood glucose was normal and sepsis screen was negative. Ultrasonography showed normal renal and adrenal size. Hormonal profile revealed normal cortisol of 12 mg/dL, adrenocorticotrophic hormone (ACTH) level 15 pg/mL, 17-hydroxyprogesterone level 17.27 ng/mL, DHEAS (dehydroepiandrosterone sulphate) 8.28 ng/mL, and elevated aldosterone levels >100 ng/mL and elevated PRA (plasma renin activity) >500 ng/mL/h (normal range 2-35 ng/mL/h). Sweat chloride was elevated (148 mEq/L). Cultures of blood and urine were sterile. CAH was ruled out and a provisional diagnosis of systemic PHA type 1b was considered. He required normal saline boluses, 3% hypertonic saline, oxygen support, intravenous fluids (dextrose-normal saline at 1.5 times maintenance) and intravenous antibiotics. Hyperkalemia was treated with sodium bicar-bonate, insulin-dextrose drip and per rectal potassium-exchange resin (calcium polystyrene sulfonate). Hydro-cortisone and fludrocortisone were tapered and dis-continued. He was discharged after 2 weeks of hospital stay on sodium supplementation at a dose of 7.5 mEq/kg/day (in the form of sodium bicarbonate suspension and 3% saline administered orally), and potassium binders (4 g/kg/day).

He was re-admitted at 7 months of age with pneumonia, acute gastroenteritis and salt losing crisis. He was managed with intravenous antibiotics and supportive therapy. At discharge, sodium supplementation was increased to 10 mEq/kg/day and potassium binders to 6 g/kg/day. He subsequently had four hospitalizations with respiratory tract infections and mild metabolic decompensation in the first two years of life, requiring high doses of sodium (20-25 mEq/kg/day) and oral potassium binders (up to 2.2 g/kg/day). Clinical exome sequencing revealed two novel heterozygous variants in *SCNN1A* gene on chromosome 12. A heterozygous single base-pair duplication in exon 7 [c.1516dup (p.Tyr506LeufsTer13)] and heterozygous single base-pair deletion in exon 3 [c.1041del. (pCys348AlafsTer42)] were identified. Both variants were novel and as they resulted in frameshift and premature truncation of protein (alpha subunit of ENaC), they were classified as pathogenic for PHA type 1b.

At present, the child is aged 5 years and has been asymptomatic for past two years. His electrolytes have remained normal on sodium supplementation at 15-20 mEq/kg/day (table salt and oral sodium bicarbonate suspension) and potassium binder (calcium polystyrene sulphonate) 1g/kg/day. His blood pressure was normal (50th-90th centile). His anthropometry and developmental milestones are age-appropriate. Biochemical profile at last follow up was normal (sodium 136 mEq/L, potassium 4.5 mEq/L).

This presentation of systemic PHA type I can be mistaken for salt-wasting CAH. Elevated aldosterone levels and PRA with normal 17 OHP can help to establish the diagnosis of PHA. Transtubular potassium gradient (TTKG) is also useful in assessment of mineralo-corticoid bioactivity in patients with hyperkalemia [2]. Cystic fibrosis (CF) is another close mimicker, as affected children may have recurrent wheezing and chest infections with poor growth in presence of a positive sweat test [3]. Secondary PHA can occur in the setting of urinary tract infections, renal dysplasia and reflux nephropathy, mandating urine culture and renal ultrasound as a part of work-up [3,4].

The management of systemic PHA remains symptomatic. Acute management includes intravenous fluids, sodium supplementation (using hypertonic saline and/or sodium bicarbonate) and potassium lowering measures. Long-term therapy comprises of oral administration of sodium up to 10-40 mmol/kg/day (hypertonic saline, table salt, oral sodium bicarbonate), along with kayexalate and low potassium diet [5]. Low potassium diets (0.5 mmol/kg/day) can be difficult to achieve with commercial formulas which contain 15-20 mmol/L of potassium. Breast milk has low potassium content (10 mmol/L) and is ideal for feeding. High doses of potassium binders (up to 8 g/kg) are often required but are poorly tolerated orally and may result in rectal bleeding or prolapse when given as enemas [5]. Children who do not tolerate these therapies may require gastrostomy tube placement. Fludrocortisone does not have a role in management because of target organ resistance to aldosterone action. Indomethacin, a potent inhibitor of prostaglandin synthesis, has been used to reduce urine output and thereby urinary sodium losses [3]. However, its exact mechanism of action is not clear and it seems to have limited role in management of hyperkalemia [5]. Synthetic peptides, like Solnatide and its congener, AP318 are novel agents, which have been shown to directly activate the mutant ENaC and hold promise for systemic PHA [6].

There is limited data on long-term follow up in patients with systemic PHA. Most patients continue to require lifelong high dose salt supplementation [7]. The clinical course among patients is variable and associated with the type of genetic mutation [8]. Patients with compound heterozygous mutations in genes encoding ENaC had less severe disease, while those with homozygous mutations suffered frequent metabolic decompensations [4,7]. The favorable disease course in the index case could be attributed to the presence of compound heterozygous mutation; however, a longer duration of follow up would be required.

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## Tele-NICU: A Possible Solution for Bridging the 'Gap'

India has around 24 million live births per year, and 20 neonates out of every 1000 live births do not live beyond neonatal period [1]. While there has been substantial improvement in NMR in last 2-3 decades, India still ranks at 121 as far as the global NMR rankings are concerned. Preterm birth and its complications (43.7%), intrapartum-related events (19.2%) and sepsis (20.8%) constitute more than 80% cases of neonatal deaths [2]. All of these causes are largely due to lack of immediate availability of skilled resources (manpower/infrastructure/knowledge) to handle the high risk births. As per the Ministry of Health's Rural Health Statistics, 2021 [3], there is an acute shortage of specialist doctors to the tune of 68% at the community health center level, all across the country. This means transferring a lot of moderate/high risk pregnancies to higher centers with neonatal intensive care units (NICUs), thus putting both mother and fetus at risk. Similarly, newly born babies with delayed-transition/ asphyxia/other issues are also referred to higher centers thus, making them face transport related risks, apart from the increased cost that comes with the transfer.

Fortunately, this distance and knowledge gap can now be bridged by creating a Tele-NICU ecosystem using currently available technology. Thus, many peripheral centers ('Spokes') can be connected with a tertiary center ('Hub') through an internet-based network, and enable evidence-based and standardized decision making and knowledge-sharing. Virtual rounds can be conducted, resuscitations attended and procedures can be guided through use of two-way audio-visual communication. Also, data from devices such as monitors, ventilators, warmers etc can be captured from the 'Spokes', and used for auditing and quality improvement purposes.

Tele-NICUs provides a platform wherein a trained neonatologist can be made available at any given time on short notice anywhere in the country be it rural, semi-rural or semi-urban hospital. The neonatologist and pediatricians can interact in real time and take rounds together, discuss treatment options, plan investigations, do teachings and establish protocols; thus, streamlining and standardizing the management. Tele-NICU services can be used for a wide range of consults, including interpreting medical data and images, confirming diagnoses, and conferring treatment plans in real time.

There is now enough evidence available to support the utility of Tele- NICU services providing care at par at the 'Spoke' centers and improve outcomes [4,5]. A recently published systematic review evaluating the impact of telemedicine on clinical outcomes in pediatric set-ups suggested that telemedicine in some form or the other resulted in decreased rate of patient transfer to higher centre (31-87.5%), shorter duration of stay (8.2 vs 15.1 days), a reduction in complications and severity of illness, and an overall lower mortality rate [6].

We surveyed some of the Tier- II cities where birthing rates are high but there is lack of quality NICU services leading to regular transfer of high risk neonates to nearby major cities. We have started operations in three cities so far viz., Kanpur (Uttar Pradesh), Panipat and Sonipat (both in Haryana), while plans for other cities are in this pipe-line. These NICUs are part of multi-specialty hospitals in these cities, but now manned and run by our institution. The central command center ('hub') is located in Gurugram. Tele-rounds are conducted twice daily from this center using a fully equipped audio/visual mobile cart with an Electronic Medical Record (EMR) software (ICCA Phillips India Inc.). Clinical rounds are carried out, and cases discussed and treatment decided after reaching consensus in an evidence-based manner. In addition, troubleshooting is also available at odd hours, as required. Regular neonatal resuscitation program (NRP) – based training sessions are conducted online for NICU staff using simulation methodology. Outreach services to other NICUs/hospitals in the 'spoke' city are also provided by our NICU team wherein, we attend high risk deliveries at birth and then transfer to the nearby 'spoke' NICU, as deemed necessary.

Thus, high quality low cost NICU services are made available through this hub-and-spoke model of tele-NICU, without the need to transfer the baby to higher centers. Preliminary results are encouraging, and other institutions are encouraged to consider adopting similar approaches.

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## Co-existing Iron Deficiency and Compliance Issues in Nutritional Macrocytic Anemia in Children

We read with interest the article by Tandon, et al. [1]. We compliment the authors for this relevant study comparing oral and parenteral vitamin B12 in macrocytic anaemia. We would like to highlight certain aspects in the study, and request clarifications from the authors.

The prevalence of dimorphic anemia in children <5 years in India is 50% [2]. It is recommended to give iron supplements during correction of nutritional B12 deficiency (dimorphic anemia) as it may unmask iron deficiency [3]. Authors have concluded that parenteral route of vitamin B12 increases hemoglobin more compared to the oral route in nutritional macrocytic anemia. A higher proportion of children being given supplemental iron in parenteral group compared to oral group (62% vs 27%), especially when 45% of cohort revealed a dimorphic peripheral blood picture, and a drop-out rate of 37.5% in oral group [1], makes this conclusion unjustified. Unexpected fall in platelet count and neutrophil count post-therapy, which ideally should increase, corroborate with above findings suggesting that correction of associated iron deficiency anemia (IDA) may have contributed to the same. Near normal median pretreatment hemoglobin (11.3 g/dL) in oral group compared to 9.4 g/dL in parenteral group also makes primary outcome of higher rise of hemoglobin in parenteral group debatable.

The cutoff for mean corpuscular volume (MCV) to define macrocytic anemia is 84+0.6×age (years) fL for children between 2-10 years and >90 fL for older children [3]. In this study [1], low median pre-treatment MCV (86 vs 84 fL) and unexpected low median fall of MCV in two groups (8.2 vs 6.1 fL) post-therapy also indicate the possibility of co-existing IDA in majority of studied subjects.

Only 10% of parenteral and 0.5-4% of oral dose of administered vitamin B12 is absorbed [4]. Also, malabsorption is an important cause of B12 deficiency and was not excluded in study. Therefore, ensuring compliance of oral preparation becomes vital. Authors have not mentioned the measures taken to ensure compliance. The oral group had high number of female children (75% vs 52%), who are more vulnerable to nutritional deprivation and poor compliance, emphasizing on the meticulous need to check compliance [5].

Rise in serum B12 without monitoring of serum methylmalonic acid (MMA) to determine treatment efficacy is a poor measure of primary outcome [3,4]. It becomes more conspicuous once both the groups were initially treated with one parenteral dose of B12. Time taken for resolution of hematological and neurological findings helps in better assessment and understanding of outcomes of therapy in macrocytic anemia.

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## AUTHORS' REPLY

We thank the readers for their interest in our work [1]. As pointed out in the opening statement regarding the higher prevalence of dimorphic anemia [2], we also agree and, in our study, 45% (36 out of 80) had dimorphic picture in the peripheral smear, and they also received additional iron supplements. Though, we had not stated this separately, 23 in group A and 13 in group B had dimorphic anemia, respectively, and accordingly, they received additional iron supplementation (62% vs 27%). So, we do not agree with the possibility of unmasking of iron deficiency.

In this study [1], the primary objective was not to compare hemoglobin levels by giving vitamin B12 but to see a rise in vitamin B12 levels when given by different routes. However, a rise in hemoglobin was found statistically better in the parenteral group accepting the limitation of not ascertaining the other underlying etiology, but appropriate nutritional counseling and folic acid supplementation were similar in both groups. In our study, both groups were advised regular out patient follow up at intervals as stated including repeating blood investigations 3 months post-treatment. Still there was higher dropout (37.5%) in the oral group, which might be explained by human behavior, i.e., not taking oral treatment seriously as compared to injectable treatment.

We agree with the comment emphasizing the meticulous need to check compliance [3]. We also agree with the possibility of coexisting iron deficiency as indicated by a fall in platelet counts and neutrophil count but a comparatively low median fall in MCV post-therapy.

We reviewed our data again regarding the underlying peripheral smear picture, which suggested 36 dimorphic vs 11 macrocytes/macro ovalocytes vs 33 normocytic red cells. In the study, the median (IQR) of age were 11 (2.3,15) and 13 (8,16) years in group A and group B, respectively. Nearly 35-40% of children did not have clinically evident pallor at the time of enrolment and the basis of enrolment was other clinical and laboratory parameters. Before enrolment, 62.5% of group A and 75% of group B already received iron therapy from an outside consultation. All these reasons also might have contributed to debatable hemoglobin changes as pointed out in this correspondence. We agree that malabsorption is an important cause of vitamin B12 deficiency, and it was mentioned in our study that we excluded children with diseases other than nutritional anemia. However, as mentioned earlier, extensive workup was not done to prove or to rule out conditions.

When this trial was undertaken, it was not common practice to give oral therapy to children; though, adults were receiving it as it was proven effective [4]. So, to avoid the ethical dilemma, it was planned to give the first dose of vitamin B12 as an injection and immediate treatment was not put on hold until the confirmation of diagnosis, and informed written consent and randomization was done subsequently. In fact, by giving first dose parenterally even in oral group, we were expecting a better rise in laboratory parameters in the oral group. Even recent recommendations mention that there is little evidence on management of vitamin B12 and folic acid in children, and it is mostly from guidelines for the adult population [5], and so, what regimen to decide on was also a difficult task. Thus, giving the first dose as an injectable was a pragmatic decision.

We agree that serum methylmalonic acid (MMA) is much more reliable for vitamin B12 deficiency, but the test was not readily available during this study. The guideline suggests that this test has a role when there is a normal or borderline vitamin B12 and discordant laboratory and clinical picture in a patient [5]. We had enrolled cases of vitamin B12 deficiency well below the deficient levels and not those with borderline or normal levels. We agree that time taken for the resolution of hematological and neurological findings helps in better assessment and understanding of outcomes of therapy in macrocytic anemia, but that was a limitation of the study as we wanted to avoid multiple pricks in children for repeated laboratory work up.

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# Colistin Resistance in Gram Negative Bacteria in a Tertiary Care Neonatal Intensive Unit in Odisha

Gram negative bacteria (GNB) like *Klebsiella* spp. and *Acinetobacter* spp. are the leading microorganisms causing neonatal sepsis, and also reported to have high rates of multidrug resistance (MDR) [1]. Clinicians have used colistimethate sodium (colistin) as last resort of treatment option for carbapenem-resistant pathogens over the last two decades [2].

We conducted an audit of the microbiological data of all blood culture-positive neonatal sepsis cases at our center between 01 January, 2017 and 30, September, 2022. The organisms were identified from blood samples by BD Bactec FX culture system (Becton Dickinson) and plating in sheep blood agar and MacConkey agar media. Species confirmation and antibiotic susceptibility were done with VITEK 2 Compact; and reported with the minimum inhibitory concentration (MIC) value for different groups of antibiotics. For interpreting antibiotics sensitivity or resistance, the guidelines of the Clinical and Laboratory Standards Institute (CLSI) were followed [3]. Multidrug resistance was defined as GNB resistant to any three of five antibiotic classes (extended-spectrum cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, and piperacillin-tazobactam). MIC value ≤2 mg/L and ≥4 mg/L were considered for labelling colistin susceptible and resistance, respectively.

During the study period, total 122 GNB were isolated from blood samples, including 34 (27.9%) *Klebsiella* spp., 26 (21.3%) *Acinetobacter* spp., 16 (13.1%) *Burkholderia* spp., 15 (12.3%) *E. coli*, 9 (7.4%) *Serratia* spp., 7 (5.7%) each of *Pseudomonas* spp. and *Enterobacter* spp., and 8 (6.5%) others. Among GNB pathogens, 30 (24.6%) were colistin resistant; *Burkholderia* spp. (15, 93.8%) and *Serratia* spp. (8, 88.9%) were the two most common pathogens with high colistin resistance. Five isolates were colistin resistant (2, *Acinetobacter* spp., 1, *E. coli*, 1, *Pseudomonas* spp., 1, *Enterobacter* spp.). Among isolated GNB, 48 (88.9%) out of 54 carbapenem resistant pathogens and 39 (72.2%) out of 54 MDR pathogens were colistin susceptible.

The reported colistin resistance in this small sample is alarming. However, three of the common pathogens *Klebsiella* spp, *Acinetobacter* spp. and *E. coli* were 93-100% colistin susceptible (including carbapenem resistance pathogens), similar to the previous studies [1,4]. The epidemiology of colistin-resistance among *Acineto-bacter* spp. and *Klebsiella* spp. from different parts of the world has been recently described [5]. Nine cases of colistin resistant *Klebsiella spp*. over twelve years were reported recently from neonatal sepsis in a neighboring state [6].

We may face more cases of colistin resistant enterobacterceae in near future due to over use of this antibiotic. As a preventive strategy, colistin should be used as reserve antibiotics at proper drug dosing under appropriate supervision for selective cases carbapenem resistance or MDR pathogens (antibiotic stewardship).

*Ethics clearance*: IEC, Kalinga institute of Medical Sciences; No. KIIMS/KIIT/IEC/83/2017 dated Sept 15, 2017.

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# REVIEWERS FOR 2022

## INDIAN PEDIATRICS

**Volume 59, January – December, 2022**

The present status of this Journal is largely dependent on the expertise and selfless cooperation of the Reviewers, whose help we gratefully acknowledge. We are indebted to them for this service.

*- Journal Committee*

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### Dental Care Guidelines for Children

The American Academy of Pediatrics has released guidelines to improve and maintain dental health in children. More than 50% of children above 6 years have at least one dental caries. What can pediatricians do to prevent this?

At the surface of teeth, there is a constant process of demineralization and remineralization. Four factors affect the balance of these opposing forces. Bacteria, sugar, saliva, and fluoride. *Streptococcus mutans* is the bacteria most implicated in dental caries and is often transmitted to children from their care givers. Hence dental caries in mothers are an important risk factor for caries in children.

Increased intake of simple sugars is a well-documented risk factor for caries. Sugary drinks, especially fruit juices, need to be restricted to less than 120 mL below 3 years and 180 mL below 6 years. Snacking between meals must be avoided. Going to bed with a bottle and bottle feeding beyond 1 year must be discouraged. Xerostomia or reduced saliva either due to disease such as Sjogren syndrome or drugs such antihistaminics may also reduce salivary flow and increase risks for caries.

The AAP recommends that twice a day brushing with a short bristled brush must be started as soon as teeth appear. Fluoride toothpaste must be encouraged. The amount of toothpaste must be limited to the size of a rice grain below 3 years and the size of a pea after 3 years. Prophylactic fluoride varnish once in 4-6 months has also been found to reduce dental caries by 33% and may be applied by pediatricians and dentists.

Healthy teeth are a lifelong blessing and pediatricians have an important role in encouraging good dental hygiene practices.

(*Pediatrics, January 2023*)

### 6-Month Oral Regime for Drug Resistant TB

The WHO has issued guidelines for the use of a shorter 6 month oral drug combination for drug resistant tuberculosis. Historically 18-20 month long therapy including injectables have been recommended for use in multi-drug resistant tuberculosis ( MDR-TB). In 2016, based on observational studies in Africa and Asia the WHO recommended shorter 9-12 month regimens. Following the STREAM trial (Standardized treatment of drug resistant tuberculosis) in 2018, it was further modified and kanamycin was replaced by amikacin. Further observational studies from South Africa enabled the WHO to recommend an all oral 9 month therapy including bedaquilone, moxifloxacin, ethionamide, ethambutol, high dose INH, pyrazinamide and clofazimine for 4 months followed by 5 months of moxifloxacin, clofazimine, ethambutol and pyrazinamide.

It was the Nix-TB phase 3 open label observational trial, which helped to establish the safety and efficacy of a 6-9 month therapy with bedaquiline, pretomanid and linazolid. Two randomized control trials in 2021 (TB-PRACTECAL and Ze-Nix) have further strengthened the evidence in favor of 6-9 month all oral regimes for MDR TB.

These guidelines have now recommended the use of a 6 month regimen of bedaquiline, pretomanid, linazolid and moxifloxacin (BPaLM) for patients above 14 years with MDR TB. It is not yet recommended for CNS, bone or military TB.

Shorter therapies and oral drugs are key in improving compliance for long drawn out therapies, as is required for tuberculosis.

(*WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment - Drug-Resistant Tuberculosis Treatment, 2022 Update*)

### Phenobarbitone vs Levetiracetam in Neonatal Seizures

Which is the better drug in neonatal seizures? Is it the older phenobarbitone (PB) or can we shift to levetiracetam (LEV)? A retrospective study of neonatal seizures from University Children's Hospital, Zurich has tried to address this vexing question.

Both preterm and term babies with EEG confirmed seizures admitted between 2011- 2022 were included into the analysis. LEV was administered at a dose of 30 mg/kg and the dose was repeated if there was no response in 30 minutes. PB was given as 20 mg/kg and repeated, if there was no response after 30 minutes, at 5mg/kg every 5 minutes upto a maximum of 20 mg/kg.

Overall 36% achieved seizure freedom after the first drug. Difference in response rates for LEV (45%) and PB (39%) were not statistically significant. However, adverse effects including hypotension, respiratory depression and sedation were commoner with PB (24%) vs LEV (1%).

A randomized controlled trial of LEV vs PB published in 2020 had supported the use of PB, which had documented a response rate of 80% compared to a mere 28% with LEV. However, that study had continuous EEG monitoring for early detection of seizures in at risk babies, which may have contributed to better responses. The better side effect profile of LEV has remained the drug's greatest selling point.
(*Pediatric Neurology, October 2022*)

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**Islet-autoantibody screening for childhood type 1 diabetes** (Lancet Diabetes Endocrinol. 2022;10:589-96)

Early prediction of childhood type 1 diabetes reduces ketoacidosis at diagnosis and provides opportunities for disease prevention. The study was conducted with the aim to identify efficient strategies for initial islet autoantibody screening in children younger than 15 years. The data was harmonized from five prospective cohorts from Finland (DIPP), Germany (BABYDIAB), Sweden (DiPiS), and the USA (DAISY and DEW-IT) into the Type 1 Diabetes Intelligence (T1DI) cohort. 24, 662 children at high risk of diabetes enrolled before age 2 years were included and followed up for islet autoantibodies and diabetes until age 15 years, or type 1 diabetes onset, whichever occurred first. Islet autoantibodies measured included those against glutamic acid decarboxylase, insulinoma antigen 2, and insulin. A total of 6722 were followed up to age 15 years or until onset of type 1 diabetes. Type 1 diabetes developed by age 15 years in 672 children, but did not develop in 6050 children. Optimal screening ages for two measurements were 2 years and 6 years, yielding sensitivity of 82% (95% CI 79–86) and PPV of 79% (95% CI 75–80) for diabetes by age 15 years. Autoantibody positivity at the beginning of each test age was highly predictive of diagnosis in the subsequent 2–5·99 year or 6–15-year age intervals. Autoantibodies usually appeared before age 6 years even in children diagnosed with diabetes much later in childhood. Thus, initial screening for islet autoantibodies at two ages (2 y and 6 y) is sensitive and efficient for public health translation but might require adjustment by country on the basis of population-specific disease characteristics.

**Neutrophil-lymphocyte and lymphocyte-monocyte ratios in type 1 diabetes for predicting future insulin need** (J Pediatr Endocrinol Metab. 2022;35:593-602)

The exact mechanism of partial clinical remission in type 1 diabetes mellitus (T1DM) has not been elucidated yet. The severity of the inflammation at the time of diagnosis may affect the occurrence or duration of this phase. The authors aimed to investigate the relationship between hematological inflammatory parameters at the time of diagnosis in T1DM and daily insulin requirement during the follow-up, and the presence of partial clinical remission period, which was determined according to insulin dose-adjusted HbA1c levels. They conducted a single center retrospective study, including children who were diagnosed with T1DM, were positive for at least one autoantibody, and were followed up for one year in their clinic between 2010 and 2020. 68 patients (56% female, 65% pre-pubertal) were included in the study. A total of 38 patients (56%) had partial clinical remission. None of the initial hematological indices were associated with the occurrence of partial remission. Initial neutrophil/lymphocyte ratio (NLR) and derived-NLR (d-NLR) levels were significantly lower and lymphocyte/monocyte ratio (LMR) levels were significantly higher in patients who showed an insulin requirement of <0.5 IU/ kg/day at the third month after diagnosis. The authors concluded that initial hematological parameters did not predict partial clinical remission period in T1DM in children, however, a lower NLR and d-NLR, or a higher LMR at the time of diagnosis can be used as an indicator of a low daily insulin need at the 3rd month of T1DM.

**Pharmacological profile of lixisenatide in children and adolescents with type 2 diabetes (**Pediatr Diab. 2022;23:641-8)

Lixisenatide, a glucagon-like peptide-1 receptor agonist has been been found to be safe and efficacious as an add-on therapy in a variety of adult patient populations. The aim of this study was to investigate the pharmacokinetic, pharmacodynamic and safety profile for the treatment of type 2 diabetes (T2D) in pediatric patients. In this Phase 1, multicenter, randomized, double-blind, placebo-controlled, parallel-group, ascending repeated dose study, participants aged 10-18 years were randomized 3:1 to receive once-daily lixisenatide in 2-week increments of 5, 10, and 20 µg (*n*=18) or placebo (*n*=5) for 6 weeks. Improvements in fasting plasma glucose, post-prandial glucose, AUC0-4.5, HbA1c, and body weight were observed with lixisenatide. Overall, the safety profile was consistent with the known profile in adults, with no unexpected side effects and no treatment-emergent adverse events resulting in death or discontinuation. The authors concluded that Lixisenatide was associated with improved glycemic control, and a good safety profile.

**Artificial intelligence for predicting risk of overweight or obesity in preschool-aged children** (Endocrine. 2022;77:63-72)

The authors adopted the machine-learning algorithms and deep-learning sequential model to determine and optimize most important factors for overweight and obesity in Chinese preschool-aged children. A cross-sectional survey was conducted enrolling children aged 3-6 years using a stratified cluster random sampling strategy. A total of 9478 children were eligible for inclusion, including 1250 children with overweight or obesity. All children were randomly divided into the training group and testing group at a 6:4 ratio. After comparison, support vector machine (SVM) outperformed the other algorithms (accuracy: 0.9457), followed by gradient boosting machine (GBM) (accuracy: 0.9454). After importance ranking, the top 5 factors seemed sufficient to obtain descent performance under GBM algorithm, including age, eating speed, number of relatives with obesity, sweet drinking, and paternal education. The authors concluded that these five factors can be fed to GBM algorithm to better differentiate children with overweight or obesity from the general children.

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## Lingua Villosa Nigra

A 14-year-old girl, who was treated for necrotizing pneumonia with intravenous antibiotics and decortication and was receiving oral linezolid and co-amoxyclav, presented with blackish discolouration of tongue and gingiva (**Fig. 1**). Linezolid was discontinued, and discoloration resolved completely over the next week.

Lingua villosa nigra, also known as black hairy tongue, is a self-limiting, usually asymptomatic lesion, characterized by the presence of elongated filiform papillae of the dorsum of the tongue, which gives a hairy appearance. It is observed following drug usage like steroids, bismuth, methylphenidate, linezolid, tetracycline, smoking and chewing tobacco, xerostomia, cocaine, poor oral hygiene, peroxide containing mouthwashes, food coloring agents, and HIV infection. Pharmacological interventions include antifungals, retinoids and mouth washes. Papillae can be clipped or removed using techniques such as CO2 laser burning and electrodesiccation. However, if it is due to medication, discontinuation will resolve the discoloration, as seen in our patient.

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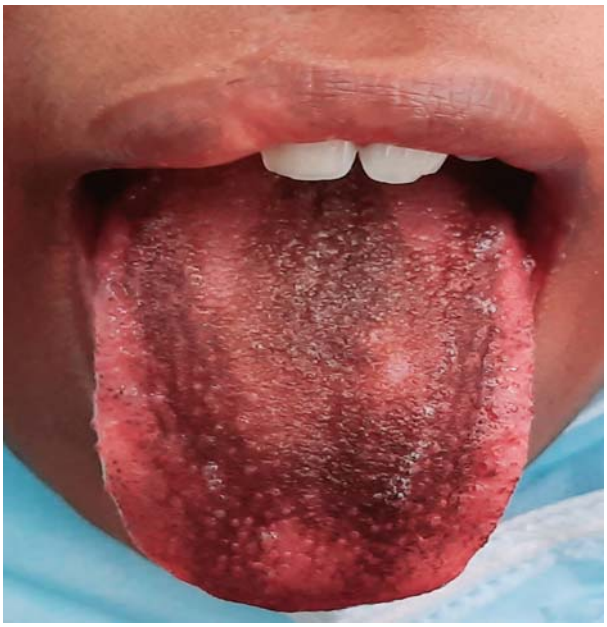
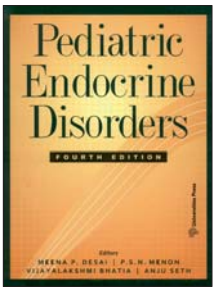


**Fig.1** Lingua villosa negra showing a black colored hairy appearance of the dorsum of tongue.

# BOOK REVIEW




**Pediatric Endocrine Disorders**
***Fourth Edition***
**MEENA P DESAI, PSN MENON, VIJAYALAKSHMI BHATIA, ANJU SETH**

*Orient BlackSwan Pvt. Ltd, Pages*: 584; *Price*: Rs. 1,895/-

Endocrine diseases in children often present as complex clinical situations for practicing pediatricians and endocrinologists. With an emphasis on practical understanding as relevant to patient care, the just-released 4th edition of this book, edited by eminent pediatric endocrinologists, aims to empower pediatricians, pediatric and adult endocrinologists, and trainees in pediatric endocrinology by providing a thorough update on common as well as rare endocrine disorders in children.

The book is well organized into 19 chapters written by distinguished Indian and International academicians. Each chapter provides an in-depth understanding of the topic, especially focusing on a stepwise and judicious approach to clinical and laboratory diagnosis of the disorder. In addition, the inclusion of topics of current and future relevance to developing countries' set-ups, such as the transition of care and community pediatric endocrinology, is a welcome addition.

The production quality of the book is good, and the text is formatted in an easy-to-understand way. Future editions may benefit from including more photographic illustrations, tables, and flow diagrams at suitable places in the chapters, which are devoid of these in the present edition.

In all, the book will serve as a comprehensive guide for the diagnosis and management of pediatric endocrine disorders with special relevance to India and other developing countries. I strongly recommend this book for practicing pediatricians, pediatric and adult endocrinologists, postgraduates in pediatrics, and allied healthcare professionals such as endocrine and diabetes nurses.

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