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Comparative analysis of developmental potentials between normal and severe acute malnourished children under-five in Pakistan: A multicenter cross-sectional study

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Abstract

Objectives: Nutritional status of children under-five children remains poor in Pakistan. Severe acute malnourished (SAM) children are at higher risk of developing development delays. This study aims to compare the developmental potential of normal and severe acute malnourished children under-five and to find sociodemographic determinants accountable for their developmental disabilities.

Setting: We conducted a multicenter cross-sectional study in three basic health units and one rural health center in Pakistan.

Participants: 200 children (SAM and healthy) aged 6 to 59 months.

Primary and secondary measures: We screened for nutritional status and clinical complications. Children underwent for developmental assessment by Denver Development Screening Tool II. A pretested structured questionnaire on sociodemographic characteristics and nutrition was used for collecting data about determinants of developmental delay.

Results: We observed statistically significant differences in anthropometric measurements among SAM compared to normal nourished in weight (M=5.39 kg, SD=1.69; vs. M=11.21 kg, SD=2.71), height (M=66.82 cm, SD=9.58; vs. M=80.6 cm, SD=12.85), mid-upper arm circumference (M=9.97 cm, SD=0.98; vs. M=14.00 cm, SD=1.19), and weight-for-height z-scores (M=-4.07, SD=1.25; vs. M=0.40, SD=1.27. SAM serves as a risk factor for delayed personal or social development, delayed fine motor development, delayed language development, delayed gross motor development and delayed global development ($p<0.001$). The logistic regression regarding developmental delays showed that among personal or social development ($p<0.001$) and language development ($p<0.05$), under-five siblings was a risk factor, while among gross motor development, mother's education ($p<0.05$) was a significant risk factor for developing this delay.

Conclusions: Our analysis indicates that children with malnutrition have a high frequency of developmental delays. Early childhood development is determined by features of the child, the family, and broader surroundings other than malnutrition.

Keywords: Developmental delay; malnutrition; under five children

Strengths and limitations of this study

- Results are based on a multicenter cross-sectional analytical study.
- The study has been conducted in three basic health units and one rural health center in the Dera Ghazi Khan district of Southern Punjab, Pakistan.
- The major limitation of this study is its cross-sectional design, which does not allow to follow up children for investigating factors that might affect the outcome.

Introduction

The word "child development" designates progression of the child in all domains of human functioning, i.e. social, cognitive, motor, hearing and speech [1]. The association between nutritional status and child development cannot be overemphasized, particularly in developing countries, as numerous studies have shown strong associations between the two [2,3]. Many children under five years of age in developing countries are subject to multiple risks: Poverty, poor health, malnutrition and the absence of a health promoting social environment adversely alter their development [1-4].

Severe acute malnutrition (SAM), or wasting as identified by the World Health Organization (WHO), is a weight-for-height z-score (WHZ) < -3 SD or a mid-upper arm circumference (MUAC) < 115 mm. It is the gravest form of under-nutrition, and, furthermore, categorized as complicated and un-complicated SAM on the footing of the presence of medical complications [5]. Children with SAM show compromised physical and cognitive development, which could depreciate their economic productivity later in life [6]. Malnutrition and developmental challenges are among the main health problems of childhood, specifically affecting developing countries [1,7]. Malnutrition not only affects physical growth, but it also results in delayed cognitive and motor growth of a child [8].

However, malnutrition is not the only factor affecting children's physical and development growth. There are further promoting as well as risk factors that play their vital role in a child's upbringing and developmental potential [1]. These risk factors are related to children's unconstructive socio-cultural or caregiving environment, meager stimulation, micronutrient deficiencies, lack of breastfeeding, housing, number of siblings, inappropriate child care, child health problems, chronic illness, family income, gender discrimination, and school facilities. All of these may have

a negative impact on attainment of a child's developmental potential. They are accountable for discrepancies in all developmental domains, such as personal social behavior, motor skills, school performance, as well as cognitive and psychomotor development [1,3].

Pakistan is one of those developing countries where the population faces numerous issues: Poverty plays a vital role as it results in poor health of children, and developmental disabilities along with malnutrition [9]. Although the chronic malnutrition or stunting rate in children under-five has dropped slightly from 43.7% in 2011 to 40.2% in 2018 in Pakistan, the indicators of acute malnutrition or wasting have deteriorated from 15.1% in 2011 to 17.7% in 2018 [9].

Despite the already available data on the nutritional profile of children under-five in Pakistan, there is still a scarcity of data which depicts how (mal-)nutrition correlates to the developmental potential of children. For that reason, the objective of this study is to compare the developmental potential of normal and severe acute malnourished children under-five and to find sociodemographic determinants accountable for developmental disabilities.

Methods

Study design and setting

A multicenter cross-sectional analytical study was conducted in three basic health units and one rural health center in the Dera Ghazi Khan district of Southern Punjab, Pakistan. This district has a high illiteracy rate and the majority of the population has a comparatively low socio-economic status. It is also a disadvantaged district with a high prevalence of malnutrition and poverty, especially among children [9]. Participants with SAM were enrolled before receiving nutritional treatment from outpatient therapeutic program centers of these health units. Healthy children were

recruited from the immunization centers and from polio campaign of the same health units who are coming for their regular immunization in the same time period.

Sample size calculation and eligibility criteria

For sample size calculation, we used a formula for cross-sectional studies taking early childhood disability prevalence (p) as 5.5% [10] and an error term (d) of 0.05. According to this, the calculated sample size was n=80 in each group. Assuming non-responses, for the sake of having a large power and allowing for sub-group analyses, we aimed to include 100 children for each group. Therefore, 200 children (boys and girls) aged 6–59 months fulfilling the inclusion criteria were enrolled in the study after written consent of parents or caregivers. The inclusion criteria for children with SAM was the presence of severe wasting as assessed by the protocols of WHO (weight-for-height < -3 SD and height-for-age < -2 SD) without any complications of malnutrition [5]. Children with physical defects, mentally retarded or clinically unfit were not included in the study. Children for the comparative group aged 6–59 months were enrolled if they had a normal nutritional status and were not suffering from any illness and disease.

Baseline assessments

A pretested questionnaire (Supplementary Appendix) including items on sociodemographic characteristics and nutritional aspects was used to obtain the information. It included information on the age of the child, gender, income, household size, immunization status of the child, parent's education, parent's profession, history of infections, weaning practices, breastfeeding and access to medical assistance. This information was obtained from mothers and caregivers at health units.

Children's gestational age was procured from the antenatal record in case of hospital delivery; and for home delivery the information was based on a maternal report. For children who were ≤24 months of age and born prematurely before 37 weeks of gestation, their age was adjusted by deducting the total weeks of missed gestation from the current age.

Anthropometric assessments

Anthropometric assessments were done by qualified nutritional supervisors who were specifically trained for these assessments. Weight was measured by using the UNISCALE nearest to the 10g by weighing children with very light cloths or if necessary without cloths. For children who were unable to stand, their weight was taken with mother by holding the child and after that weight of the mother was excluded. Length of the child was assessed nearest to 0.1 cm with the help of a length measuring board ("SECA GmbH & Co. KG, Hamburg, Germany"). Those children who could stand and were >87 cm in height, their height was measured at a standing position without shoes. Weight-for-height z-scores were counted according to the WHO child growth standards with WHO ANTHRO, version 3.2.2.

Developmental assessment

Children after completing eligibility criteria underwent a development assessment with the help of a pediatrician by following the Denver Development Screening Tool II (DDST II). This development tool evaluates the child's ability until six years of age to perform a variety of different tasks and then compares them with a standardized populace of children of similar age. Tasks are categorized into four domains: personal and social development, fine motor milestones, language

skills, and gross motor milestones. On the basis of these domains, final developmental status of children was concluded [11].

Statistical analyses

The data collected was entered and analyzed using SPSS version 23.0. The quantitative variables were expressed using means and standard deviations, while categorical variables were expressed as frequencies and percentages. The Chi-square test was applied to find associations of various factors among the two studied groups of children (SAM vs. normal). The independent Student's t-test was applied to see the relationship between groups of quantitative variables. Logistic regression was applied to investigate potential risk factors for various development delays. These results are presented in terms of Odds ratios (OR) with 95% Confidence intervals (CI). For all analyses, a p-value <0.05 was considered as statistically significant.

Patient and public involvement

Neither patients nor public have been involved in the study.

Results

About half (48.5%) of the mothers of the study sample had no formal schooling. Of the 200 children, there were 32% who had received exclusive breastfeeding. Gender was distributed almost equal (101 males and 99 females). Overall, the children had a mean (SD) age of 21.27 (14.25) months (Table 1). Table 1 compares the characteristics between SAM and normal children. According to this, the mean (SD) age among SAM children was 16.09 (11.16) months and among normal children was 26.44 (15.15) months. Furthermore, all sociodemographic variables

(education of mothers, number of under five siblings, exclusive breastfeeding), as well as anthropometric characteristics such as mean weight, height, and MUAC among SAM was lower than in normal children. The developmental delay regarding personal or social development, fine motor development, language development, gross motor development and global development was higher in SAM children than in normal children.

Table 1: Sociodemographic characteristics, anthropometric measurements and developmental status of severe acute malnourished and normal children (n=200)

		Severe acute malnourished (n=100)	**Normal (n=100)**
Sociodemographic characteristics		**%**	**%**
Gender	Male	48	53
	Female	52	47
Mother's education	Illiterate	64	33
	Primary and above	36	67
Under five siblings	2 and less	83	53
	3 and more	17	47
Exclusive breastfeeding	Yes	17	47
	No	83	53
Anthropometry		**Mean (SD)**	**Mean (SD)**
Weight (kg)		5.39 (1.69)	11.21 (2.71)
Height (cm)		66.82 (9.58)	80.60 (12.85)
MUAC (cm)		9.97 (0.98)	14.00 (1.19)
Weight-for-height z-score		-4.07 (1.25)	0.40 (1.27)
Weight-for-age z-score		-4.64 (1.07)	-0.58 (2.79)
Height-for-age z-score		-3.94 (1.41)	-1.04 (5.13)
Developmental status		**%**	**%**
Delayed personal or social development		69	11
Delayed fine motor development		39	8
Delayed language development		32	8
Delayed gross motor development		34	10
Delayed global development		66	20

Notes: SD=Standard deviation; MUAC=Mid-upper arm circumference

The means for anthropometric measurements like weight, height, MUAC, and weight-for-height z-scores were statistically significant when compared in SAM and normal children ($p<0.001$). SAM serves as a risk factor for delayed personal or social development, delayed fine motor development, delayed language development, delayed gross motor development and delayed global development as shown by odds ratio. All of the above factors were also statistically significant ($p<0.001$) (Table 2).

Table 2: Association of nutritional status among severe acute malnourished and normal children regarding anthropometric measurements and developmental status (n=200)

	SAM (n=100)	**Normal (n=100)**	
Anthropometric measurements	**Mean (SD)**	**Mean (SD)**	**MD / t-test value**
Weight (kg)	5.38 (1.69)	11.21 (2.71)	-5.83 / -18.26**
Height (cm)	66.82 (9.58)	80.6 (12.85)	-13.78 / -8.60**
MUAC (cm)	9.97 (0.982)	14.0 (1.19)	-4.03 / -26.10**
Weight-for-height z-score	-4.07 (1.25)	0.40 (1.27)	-4.48 / -25.09**
Developmental status	**%**	**%**	**OR (95% CI)**
Delayed personal or social development	69	11	18.01 (8.45–38.37)**
Delayed fine motor development	39	8	7.35 (3.22–16.81)**
Delayed language development	32	8	5.41 (2.35–12.48)**
Delayed gross motor development	34	10	4.64 (2.14–10.05)**
Delayed global development	66	20	7.767 (4.09–14.74)**

Notes: SAM=Severe acute malnutrition; OR=Odds ratio; MD=Mean difference; SD=Standard deviation; *p<0.05; **p<0.001

The logistic regression regarding developmental delays and sociodemographic variables showed that among personal or social development ($p<0.001$) and language development ($p<0.05$), the number of under five siblings was risk factor. Mother's education was significantly associated with a delay in gross motor development ($p<0.05$) (Table 3).

Table 3: Logistic regression between sociodemographic characteristics and nutritional status of children (n=200)

Developmental delays		OR (95% CI)	B	Adjusted OR (95% CI)
Personal or social development	Mother's education	3.68 (0.90–15.07)	0.208	1.23 (0.68–2.24)
	Gender	0.59 (0.16–2.19)	0.189	1.208 (0.67–2.19)
	Under five siblings	4.36 (1.04–18.25)**	1.451	4.27 (2.08–8.74)**
Fine motor development	Mother's education	3.33 (0.69–16.16)	0.641	1.90 (0.97–3.73)
	Gender	0.51 (0.11–2.46)	-0.08	0.92 (0.47–1.79)
	Under five siblings	5.50 (1.07–28.25)**	0.621	1.86 (0.85–4.07)
Language development	Mother's education	1.89 (0.39–9.27)	-0.03	0.97 (0.48–1.97)
	Gender	0.60 (0.12–2.94)	0.132	1.14 (0.57–2.31)
	Under five siblings	1.80 (0.28–11.60)	0.969	2.64 (1.09–6.38)*
Gross motor development	Mother's education	1.22 (0.29–5.20)	0.739	2.09 (1.04–4.24)*
	Gender	1.05 (0.25–4.42)	-0.515	0.60 (0.30–1.20)
	Under five siblings	5.00 (0.97–25.77)	0.832	2.30 (0.99–5.35)

Notes: OR=Odds ratio; *p<0.05; **p<0.001

Discussion

The results show that the frequency of developmental disabilities among severe acute malnourished children aged 6–59 months is alarmingly high compared to their well-nourished counterparts in the study area of Punjab province in Pakistan. These SAM children were performing poorly in all domains of developmental milestones, particularly in personal and social development. These results are comparable with previous studies as it was proved that protein energy malnutrition in children is one of the main reasons for alteration in brain development. This results in a reduction of brain size, dendritic arborization and cell maturation, which subsequently leads to behavioural consequences producing social and behavioural disabilities that also affect child's adulthood [12].

SAM children also showed a decreased developmental potential in language and motor milestones. It has been stated that children who suffered from SAM in the initial years of life showed

developmental delay in all domains. A critical feature of malnutrition is the deficiency of different micronutrients – including iron, folate, vitamin A, and zinc – that are important for growth and development, particularly for cognitive functioning and brain development [3,13]. A deficiency in calcium and vitamin D may result in delayed motor milestones. The developing brain of children is particularly susceptible to nutritional insults and nutritional deficiency even in the acute phase, cause impairment in normal functioning of the middle ear, affecting negatively the entire auditory system causing delay in speech and hearing domains. These children were then prone to face difficulties in verbal and written language [14,15].

Early childhood development is also determined by features of the child, the family, and broader surroundings other than malnutrition. In our study, we have also tried to find out these features responsible for developmental delays in children. We found that mother's education showed significant associations with the developmental potential of children. There were more illiterate mothers among the SAM group. Illiteracy causes lots of problems in understanding the effect of malnutrition on the development of their children. These study findings are consistent with results of a study that showed a positive association between illiteracy of the mothers with the development of acute malnutrition [12].

Another determinant of delayed development was the number of under five siblings. Zhang et al. [4] concluded in their study that developmental delays were associated with parenting, particularly meager stimulation, caregiver sensitivity, and emotional warm and responsive feeding for children. According to this, one might expect that an increased number of children limits the ability to pay proper care to each child which is required for their normal growth and development [4].

We found that the frequency of children not receiving exclusive breastfeeding was much higher in the SAM group (55%) compared to the normal group (6%). Findings from previous studies

concluded that exclusive breastfeeding is one of the major factors preventing different forms of childhood malnutrition [2,3]. Studies also correlate breastfeeding with high score achievement in cognitive tests and in motor and mental development because of breast milk being rich in long chain polyunsaturated fatty acids, and breast milk stimulates brain development, predominantly white matter growth [3].

Limitations

Our study has some limitation as it is cross-sectional. We did not follow up children for investigating factors that might affect the outcome. Observing the children's developmental and nutritional status in longitudinal studies would give a better insight of the dynamic nature of growth and development in children. However, the strength of our study is that we have used the Denver developmental screening test [11], which is a validated scale for developmental assessment of children. Furthermore, data collection has been conducted by well-trained medical staff by using established protocols.

Conclusion

In conclusion, our findings showed that SAM children have a high frequency of developmental disabilities in comparison with their well-nourished children in all domains. Mother's education and the number of under five siblings were also significantly associated with delayed development in this vulnerable group.

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Conflicts of interest:

The authors declare that they have no conflict of interest.

Funding:

None

Data sharing:

Data is available upon reasonable request from the corresponding author.

Ethical considerations:

Ethical approval of the current study was obtained from the Ethical Review and Advanced Study Research Board of the University of Punjab, Pakistan (Ref.: 9/2352-ACAD), and the District Health Office of the Dera Ghazi Khan, Punjab, Pakistan. Written informed consent was obtained from caregivers or parents.

Author contributions:

Conceptualization: J.S. and R.Z.; formal analysis: J.S.; investigation: J.S., R.Z., F.M. and G.M.J.B.; supervision: F. F.; writing—original draft preparation: J.S..; writing—review and editing: R.Z., F.M., G.M.J.B. and F.F. All authors have read and agreed to the published version of the manuscript.

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COMPARATIVE ANALYSIS OF DEVELOPMENTAL POTENTIAL BETWEEN NORMAL AND SEVERE ACUTE MALNOURISHED UNDER FIVE CHILDREN IN PAKISTAN: A MULTICENTER CROSS SECTIONAL STUDY

QUESTIONNAIRE

CONSENT FORM IN ENGLISH

Description of the Research and Your Participation

You are invited to participate in a research study conducted by Dr. Javeria Saleem. The purpose of this research is to evaluate the developmental potential between normal and severe acute malnourished under five children in Pakistan.

Potential benefits
Early detection of developmental potential delays helps to prioritize the programs for minimizing the effect of these delay to perform daily activities in efficient manner among malnourished children.

Protection of confidentiality
We will do everything we can to protect your privacy. Your identity will not be revealed in any publication resulting from this study.

Voluntary participation
Your participation in this research study is voluntary. You may choose not to participate and you may withdraw your consent to participate any time. You will not be penalized in any way should you decide not you participate or to withdraw from this study.

CONSENT

I have read this consent form and have been given the opportunity to ask questions. I give my consent to participate in this study.

Participant's signature _____ Date: _____

A copy of this consent form should be given to the participant.

QUESTIONNAIRE

Sociodemographic factors

1. Name of respondent _____

2. Father's name _____

3. Contact number _____

4. Age of the baby (months) _____

5. Gender: Male Female

6. Child's gestational age > 37 weeks < 37weeks

7. Mother's education _____

8. Father's education _____

9. Monthly income of family _____

10. Number of under-five siblings _____

11. Household member number _____

12. Exclusive breastfeeding: Yes No

13. Age of starting of semi solid diet _____

Anthropometric Measurements

14. Weight (kg) _____

15. Height (cm) _____

16. MUAC (cm) _____

17. Weight-for-height Z-score _____

18. Weight-for-age Z-score _____

19. Height-for-age Z-score _____

Group:

20. SAM _____ Normal _____

Denver Developmental Screening Tool II

21. Personal or social development:	Delayed	Normal
22. Fine motor development:	Delayed	Normal
23. Language development:	Delayed	Normal
24. Gross motor development:	Delayed	Normal
25. Global development:	Delayed	Normal

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	5-6, 8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6-8
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Comparative analysis of developmental profile between normal and severe acute malnourished under-five children in Pakistan: A multi-center cross-sectional study

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Abstract

Objectives: This study aims to compare the developmental profile of severe acute malnourished (SAM) and normal under-five children and to find socio-demographic determinants accountable for their developmental disabilities.

Setting: We conducted a multi-center cross-sectional study in three basic health units and one rural health centre in Pakistan.

Participants: 200 children (SAM and healthy) aged 6 to 59 months.

Primary and secondary measures: We screened for nutritional status and clinical complications. Children underwent for developmental assessment by Denver Development Screening Tool II. A pretested structured questionnaire on sociodemographic characteristics and nutrition was used for collecting data about determinants of developmental delay.

Results: We observed statistically significant differences in anthropometric measurements among SAM compared to normal nourished in weight, height, mid-upper arm circumference and weight-for-height z-scores. SAM serves as a significant risk factors ($p<0.001$) for delayed personal or social development (69% vs. 11%; OR [95% CI] = 18.01 [8.45–38.37]), delayed fine motor development (39% vs. 8%; OR [95% CI] = 7.35 [3.22–16.81]), delayed language development (32% vs. 8%; OR [95% CI] = 5.41 [2.35–12.48]), delayed gross motor development (34% vs. 10%; OR [95% CI] = 4.64 [2.14–10.05]) and delayed global development (66% vs. 20%; OR [95% CI] = 7.77 [4.09–14.74]). Applying logistic regression, personal or social development ($p<0.001$) and language development ($p<0.05$), under-five siblings was a risk factor, while among gross motor development, mother's educational status ($p<0.05$) was a significant risk factor for developmental delay.

Conclusions: Our analysis indicates that children with malnutrition have a high frequency of developmental delays. Missing maternal education and a higher number of under-five siblings are also potential risk factors for developmental delay.

Keywords: Developmental delay; malnutrition; under five children

Strengths and limitations of this study

- Results are based on a multicenter cross-sectional analytical study.
- The study has been conducted in three basic health units and one rural health centre in the Dera Ghazi Khan District of Southern Punjab, Pakistan.
- The major limitation of this study is its cross-sectional design, which does not allow for follow up children for investigating factors that might affect the outcome.

Introduction

The word "child development" designates progression of the child in all domains of human functioning, i.e. social, cognitive, motor, hearing and speech [1]. Global statistics from World Health Organization (WHO) showed that an estimated 45.4 million children under five, which are 6.7% of total under five, suffered from wasting, while 149.2 million children (22%) suffered from stunting in 2021 [2]. Globally, children with severe malnutrition also contribute to more than one million under five deaths annually [3]. Regarding delayed developmental potential, UNICEF estimates of 2016 showed that more than 43% children under five are not up to the mark and as per World Bank statistics, around 250 million children in low- and middle-income countries are having risk of delayed developmental potential. The reasons behind this could be poverty, poor nutrition as well as stunting (or less than standard height for age) [4, 5]. The association between nutritional status and child development cannot be overemphasized, particularly in developing countries, as numerous studies have shown strong associations between the two [6,7]. Many children under five years of age in developing countries are subject to multiple risks: poverty, poor health, malnutrition and the absence of a health promoting social environment adversely alter their development [6-8]. A study from Jamaica showed that interventions of educating mothers in their primary care strategies regarding rearing of undernourished children provides significant results in the development of children with their hearing and speech, overall performance as well as coordination between hand and eyes [9].

Severe acute malnutrition (SAM), as identified by the World Health Organization (WHO), is a "weight-for-height z-score (WHZ) < -3 SD of the median WHO growth standards or a mid-upper-arm circumference (MUAC) < 115 mm, by visible severe wasting or presence of nutritional oedema". It is the gravest form of under-nutrition, and, furthermore, categorized as complicated

and un-complicated SAM on the footing of the presence of medical complications [10]. Malnutrition and developmental challenges are among the main health problems of childhood, specifically affecting developing countries [1, 10]. Malnutrition not only affects physical growth, but it also results in delayed cognitive and motor growth of a child [11-13].

However, malnutrition is not the only factor affecting children's physical and development growth. There are further promoting as well as risk factors that play their vital role in a child's upbringing and developmental potential [1]. These risk factors are related to children's unconstructive socio-cultural or caregiving environment, meagre stimulation, micronutrient deficiencies, lack of breastfeeding, housing, number of siblings, inappropriate child care, child health problems, chronic illness, family income, gender discrimination, and school facilities. All of these may have a negative impact on attainment of a child's developmental potential. They are accountable for discrepancies in all developmental domains, such as personal social behaviour, motor skills, school performance, as well as cognitive and psychomotor development [1, 7].

Pakistan is one of those developing countries where the population faces numerous issues: Poverty plays a vital role as it results in poor health of children, and developmental disabilities along with malnutrition [14]. Although the chronic malnutrition or stunting rate in children under-five has dropped slightly from 43.7% in 2011 to 40.2% in 2018 in Pakistan, the indicators of acute malnutrition or wasting have deteriorated from 15.1% in 2011 to 17.7% in 2018 [14].

Despite the already available data on the nutritional profile of children under-five in Pakistan, there is still a scarcity of data which depicts how malnutrition correlates to the development of children. For that reason, the core objectives of this study are to compare the development of normal and severe acute malnourished under-five children, and to find socio-demographic determinants accountable for developmental disabilities.

Methods

Study design and setting

A multi-center cross-sectional analytical study was conducted in Outpatient Therapeutic Programme (OTP) Centres situated in three basic health units (BHUs) and one rural health centre (RHC) in the Dera Ghazi Khan District of Southern Punjab, Pakistan. This district has a high illiteracy rate and the majority of the population has a comparatively low socio-economic status. It is also a disadvantaged district with a high prevalence of malnutrition and poverty, especially among children [14].

Out of 16 OTP Centres in the Dera Ghazi Khan region, as per recommendations of the District Health Office, a total of four centres (three BHUs and one RHC) were selected. The recommendation implies that these centres were actively functioning in terms of staff members as well as availability of therapeutic food. Moreover, these selected centres were being used as screening centres for assessing nutritional status of the infants and children for timely recognition and also referring them in case of complications to other tertiary care facilities.

Participants with SAM were enrolled before receiving nutritional treatment from outpatient therapeutic program centres of these health units. Healthy children were recruited from the immunization centres and from polio campaign of the same health units who are coming for their regular immunization in the same time period.

Sample size calculation and eligibility criteria

For sample size calculation, we used a formula for cross-sectional studies taking early childhood disability prevalence (p) as 5.5% [15] and an error term (d) of 0.05. According to this, the

calculated sample size was n=80 in each group. Assuming non-responses, for the sake of having a large power and allowing for sub-group analyses, we aimed to include 100 children for each group. Therefore, 200 children (boys and girls) aged 6–59 months fulfilling the inclusion criteria were enrolled in the study after written consent of parents or caregivers (Figure 1). The inclusion criteria for children with SAM was the presence of severe wasting as assessed by the protocols of WHO (weight-for-height < -3 SD and height-for-age < -2 SD) without any complications of malnutrition [8]. Children with physical defects, mentally retarded or clinically unfit were not included in the study. Children for the comparative group aged 6–59 months were enrolled if they had a normal nutritional status and were not suffering from any illness and disease.

Baseline assessments

A pretested questionnaire (Supplementary Appendix) including items on sociodemographic characteristics and nutritional aspects was used to obtain the information. It included information on the age of the child, gender, income, household size, and immunization status of the child, parent's education, and parent's profession, history of infections, weaning practices, breastfeeding and access to medical assistance. This information was obtained from mothers and caregivers at health units.

Children's gestational age was procured from the antenatal record in case of hospital delivery; and for home delivery the information was based on a maternal report. For children who were ≤24 months of age and born prematurely before 37 weeks of gestation, their age was adjusted by deducting the total weeks of missed gestation from the current age.

Anthropometric assessments

Anthropometric assessments were done by qualified nutritional supervisors who were specifically trained for these assessments. Weight was measured by using the UNISCALE nearest to the 10g by weighing children with very light cloths or if necessary without cloths. For children who were unable to stand, their weight was taken with mother by holding the child and after that weight of the mother was excluded. Length of the child was assessed nearest to 0.1 cm with the help of a length measuring board ("SECA GmbH & Co. KG, Hamburg, Germany"). Those children who could stand and were >87 cm in height, their height was measured at a standing position without shoes. The quality of the measurements was accomplished using two times measurement procedure and taking average of the two figures. Weight-for-height z-scores were counted according to the WHO child growth standards with WHO ANTHRO, version 3.2.2.

Developmental assessment

Children after completing eligibility criteria underwent a development assessment with the help of a paediatrician by following the Denver Development Screening Tool II (DDST II). This development tool evaluates the child's ability until six years of age to perform a variety of different tasks and then compares them with a standardized populace of children of similar age. 125 Tasks are categorized into four domains: personal and social development, fine motor milestones, language skills, and gross motor milestones. These four categories include tasks such as recognizing people and also start care for their personal needs (*personal and social development*); coordination of eyes and hands, problem solving as well as tearing the papers apart (*fine motor skills*); understanding, hearing and saying words (*language*); walking, sitting, jumping and using of large muscles (*gross motor skills*). On the basis of these domains, final developmental status of children was concluded [16].

Statistical analyses

The data collected was entered and analysed using SPSS version 23.0. The quantitative variables were expressed using means and standard deviations, while categorical variables were expressed as frequencies and percentages. The Chi-square test was applied to find associations of various factors among the two studied groups of children (SAM vs. normal). The independent Student's t-test was applied to see the relationship between groups of quantitative variables. Logistic regression was applied to investigate potential risk factors for various development delays. These results are presented in terms of Odds ratios (OR) with 95% Confidence intervals (CI). For all analyses, a p-value <0.05 was considered as statistically significant.

Patient and public involvement

Neither patients nor public have been involved in the study.

Results

About half (48.5%) of the mothers of the study sample had no formal schooling. Of the 200 children, there were 32% who had received exclusive breastfeeding. Gender was distributed almost equal (101 males and 99 females). Overall, the children had a mean (SD) age of 21.27 (14.25) months (Table 1). Table 1 compares the characteristics between SAM and normal children. According to this table, the mean (SD) age among SAM children and normal children was 16.09 (11.16) months and 26.44 (15.15) months respectively. Furthermore, all socio-demographic variables (education of mothers, number of under five siblings, exclusive breastfeeding), as well as anthropometric characteristics such as mean weight, height, and MUAC among SAM was lower than in normal children. The developmental delay regarding personal or social development, fine

motor development, language development, gross motor development and global development was higher in SAM children than in normal children.

Table 1: Socio-demographic characteristics, anthropometric measurements and developmental status of severe acute malnourished and normal children (n=200)

		Severe acute malnourished (n=100)	**Normal (n=100)**
Socio-demographic characteristics		**%**	**%**
Gender	Male	48	53
	Female	52	47
Mother's education	Illiterate	64	33
	Primary and above	36	67
Under five siblings	2 and less	83	53
	3 and more	17	47
Exclusive breastfeeding	Yes	17	47
	No	83	53
Age mMonths) Mean±SD		16.09±11.16	26.44±15.15
Anthropometry		**Mean (SD)**	**Mean (SD)**
Weight (kg)		5.39 (1.69)	11.21 (2.71)
Height (cm)		66.82 (9.58)	80.60 (12.85)
MUAC (cm)		9.97 (0.98)	14.00 (1.19)
Weight-for-height z-score		-4.07 (1.25)	0.40 (1.27)
Weight-for-age z-score		-4.64 (1.07)	-0.58 (2.79)
Height-for-age z-score		-3.94 (1.41)	-1.04 (5.13)
Developmental status		**%**	**%**
Delayed personal or social development		69	11
Delayed fine motor development		39	8
Delayed language development		32	8
Delayed gross motor development		34	10
Delayed global development		66	20

Notes: SD=Standard deviation; MUAC=Mid-upper arm circumference

The means for anthropometric measurements like weight, height, MUAC, and weight-for-height z-scores were statistically significant when compared in SAM and normal children ($p<0.001$).

SAM serves as a risk factor for delayed personal or social development, delayed fine motor development, delayed language development, delayed gross motor development and delayed global development as shown by odds ratio. All of the above factors were also statistically significant ($p<0.001$) (Table 2).

Table 2: Association of nutritional status among severe acute malnourished and normal children regarding anthropometric measurements and developmental status (n=200)

	SAM (n=100)	**Normal (n=100)**	
Anthropometric measurements	**Mean (SD)**	**Mean (SD)**	**MD / t-test value**
Weight (kg)	5.38 (1.69)	11.21 (2.71)	-5.83 / -18.26**
Height (cm)	66.82 (9.58)	80.6 (12.85)	-13.78 / -8.60**
MUAC (cm)	9.97 (0.982)	14.0 (1.19)	-4.03 / -26.10**
Weight-for-height z-score	-4.07 (1.25)	0.40 (1.27)	-4.48 / -25.09**
Developmental status	**%**	**%**	**OR (95% CI)**
Delayed personal or social development	69	11	18.01 (8.45–38.37)**
Delayed fine motor development	39	8	7.35 (3.22–16.81)**
Delayed language development	32	8	5.41 (2.35–12.48)**
Delayed gross motor development	34	10	4.64 (2.14–10.05)**
Delayed global development	66	20	7.767 (4.09–14.74)**

Notes: SAM=Severe acute malnutrition; OR=Odds ratio; MD=Mean difference; SD=Standard deviation; **p<0.001

The logistic regression regarding developmental delays and socio-demographic variables showed that among personal or social development ($p<0.001$) and language development ($p<0.05$), the number of under five siblings was risk factor. Mother's education was significantly associated with

a delay in gross motor development ($p<0.05$) and exclusive breastfeeding were significantly associated with personal or social development (Table 3).

Table 3: Logistic regression between socio-demographic characteristics and nutritional status of children (n=200)

Developmental delays			SAM (%)	Normal (%)	OR (95% CI)	β	Adjusted OR (95% CI)
Personal or social development	Mother's education	No education	40	3	3.68 (0.90–15.07)	0.208	1.23 (0.68–2.24)
		Primary and above	29	8			
	Gender	Male	35	7	0.59 (0.16–2.19)	0.189	1.208 (0.67–2.19)
		Female	34	4			
	Under five siblings	2 and lower	61	7	4.36 (1.04–18.25)**	1.451	4.27 (2.08–8.74)**
		3 and higher	8	4			
	Exclusive Breast Feeding	No	55	6	3.27 (0.87-12.3)*	1.326	3.08 (1.78–5.69)**
		Yes	14	5			
Total			69	11			
Fine motor development	Mother's education	No education	26	3	3.33 (0.69–16.16)	0.641	1.90 (0.97–3.73)
		Primary and above	13	5			
	Gender	Male	18	5	0.51 (0.11–2.46)	-0.08	0.92 (0.47–1.79)
		Female	21	3			
	Under five siblings	2 and lower	33	4	5.50 (1.07–28.25)**	0.621	1.86 (0.85–4.07)
		3 and higher	6	4			
Total			39	8			
Language development	Mother's education	No education	17	3	1.89 (0.39–9.27)	-0.03	0.97 (0.48–1.97)
		Primary and above	15	5			
	Gender	Male	16	5	0.60 (0.12–2.94)	0.132	1.14 (0.57–2.31)
		Female	16	3			
	Under five siblings	2 and lower	27	6	1.80 (0.28–11.60)	0.969	2.64 (1.09–6.38)*
		3 and higher	5	2			
Total			32	8			
Gross motor development	Mother's education	No education	22	6	1.22 (0.29–5.20)	0.739	2.09 (1.04–4.24)*
		Primary and above	12	4			
	Gender	Male	14	4	1.05 (0.25–4.42)	-0.515	0.60 (0.30–1.20)
		Female	20	6			
	Under five siblings	2 and lower	30	6	5.00 (0.97–25.77)	0.832	2.30 (0.99–5.35)
		3 and higher	4	4			
Total			34	10			

Notes: OR=Odds ratio; *p<0.05; **p<0.001

Discussion

The results show that the frequency of developmental disabilities among severe acute malnourished children aged 6–59 months is alarmingly high compared to their well-nourished counterparts in the study area of Punjab province in Pakistan. The SAM children enrolled in the study were performing poorly in all domains of developmental milestones, particularly in personal and social development. These results are comparable with previous studies as it was proved that severe malnutrition in children is one of the main reasons for alteration in brain development. This results in a reduction of brain size, dendritic arborisation and cell maturation, which subsequently leads to behavioural consequences producing social and behavioural disabilities that also affect child's adulthood [17].

Children with SAM show compromised physical and cognitive development, which could depreciate their economic productivity later in life [11]. During their first two years life, children are vulnerable due to higher body mass ratio. Rapid physical structure increases the need for nutritional requirements and also could face infection risks [18]. Mortality numbers reduction due to SAM remains the priority for most and also survival rates are increasing with favourable outcomes [11]. A systematic review consisting of fifteen studies that included literature from Barbados and Mauritius large cohorts found significant results between SAM and various cognitive disabilities including problem solving, having short-term memory, working memory, intelligent Quotient (IQ), cognitive processing along with academic skills [18-20].

SAM children also showed a decreased developmental potential in language and motor milestones. It has been stated that children who suffered from SAM in the initial years of life showed developmental delay in all domains. A critical feature of malnutrition is the deficiency of different

micronutrients – including iron, folate, vitamin A, and zinc – that are important for growth and development, particularly for cognitive functioning and brain development [7, 21]. A deficiency in calcium and vitamin D may result in delayed motor milestones. The developing brain of children is particularly susceptible to nutritional insults and nutritional deficiency even in the acute phase, cause impairment in normal functioning of the middle ear, affecting negatively the entire auditory system causing delay in speech and hearing domains. These children were then prone to face difficulties in verbal and written language [22, 23].

Early childhood development is also determined by features of the child, the family, and broader surroundings other than malnutrition. In our study, we have also tried to find out these features responsible for developmental delays in children. We found that mother's education showed significant associations with the developmental potential of children. There were more illiterate mothers among the SAM group. Illiteracy causes lots of problems in understanding the effect of malnutrition on the development of their children. These study findings are consistent with results of a study that showed a positive association between illiteracy of the mothers with the development of acute malnutrition [17].

Another determinant of delayed development was the number of under five siblings. Zhang et al. [8] concluded in their study that developmental delays were associated with parenting, particularly meagre stimulation, caregiver sensitivity, and emotional warm and responsive feeding for children. According to this, one might expect that an increased number of children limits the ability to pay proper care to each child which is required for their normal growth and development [8].

We found that the frequency of children not receiving exclusive breastfeeding was much higher in the SAM group (55%) compared to the normal group (6%). Findings from previous studies concluded that exclusive breastfeeding is one of the major factors preventing different forms of

childhood malnutrition [6, 7]. Studies also correlate breastfeeding with high score achievement in cognitive tests and in motor and mental development because of breast milk being rich in long chain polyunsaturated fatty acids, and breast milk stimulates brain development, predominantly white matter growth [7].

Limitations

Our study has some limitation as it is cross-sectional. We did not follow up children for investigating factors that might affect the outcome. Observing the children's developmental and nutritional status in longitudinal studies would give a better insight of the dynamic nature of growth and development in children. Another limitation of our study is that factors like children's caregiving environment, meagre stimulation, micronutrient deficiencies and lack of breastfeeding were not assessed. However, the strength of our study is that we have used the Denver developmental screening test [16], which is a validated scale for developmental assessment of children. Furthermore, data collection has been conducted by well-trained medical staff by using established protocols.

Conclusion

In conclusion, our findings showed that SAM children have a high frequency of developmental disabilities in comparison with their well-nourished children in all domains. No education of mother and the higher number of under five siblings were also significantly associated with delayed development in this vulnerable group. Moreover, screening in under-five children is not part of the regular protocol in Pakistan. Therefore, this study will be helpful for policymakers to add this screening as a routine care.

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Conflicts of interest:

The authors declare that they have no conflict of interest.

Funding:

None

Data sharing:

Data is available upon reasonable request from the corresponding author.

Ethical considerations:

Ethical approval of the current study was obtained from the Ethical Review and Advanced Study Research Board of the University of Punjab, Pakistan (Ref.: 9/2352-ACAD), and the District Health Office of the Dera Ghazi Khan, Punjab, Pakistan. Written informed consent was obtained from caregivers or parents.

Author contributions:

Conceptualization: J.S. and R.Z.; formal analysis: J.S.; investigation: J.S., R.Z., F.M. and G.M.J.B.; supervision: F. F.; writing—original draft preparation: J.S..; writing—review and editing: R.Z., F.M., G.M.J.B. and F.F. All authors have read and agreed to the published version of the manuscript.

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Levels and trends in child malnutrition: UNICEF/WHO/The World Bank Group joint child malnutrition estimates: key findings of the 2021 edition 2021.

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Figure 1: Flowchart

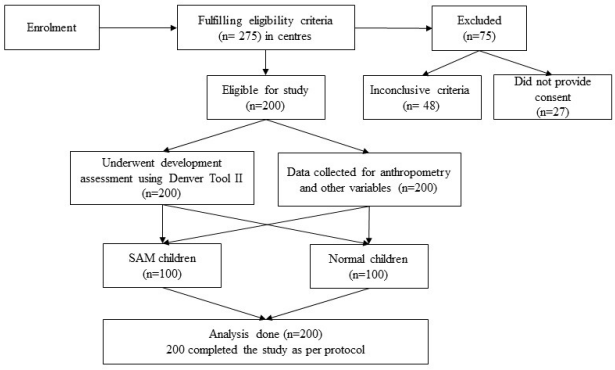

Figure 1: Flowchart

338x190mm (96 x 96 DPI)

COMPARATIVE ANALYSIS OF DEVELOPMENTAL POTENTIAL BETWEEN NORMAL AND SEVERE ACUTE MALNOURISHED UNDER FIVE CHILDREN IN PAKISTAN: A MULTICENTER CROSS SECTIONAL STUDY

QUESTIONNAIRE

CONSENT FORM IN ENGLISH

Description of the Research and Your Participation

You are invited to participate in a research study conducted by Dr. Javeria Saleem. The purpose of this research is to evaluate the developmental potential between normal and severe acute malnourished under five children in Pakistan.

Potential benefits
Early detection of developmental potential delays helps to prioritize the programs for minimizing the effect of these delay to perform daily activities in efficient manner among malnourished children.

Protection of confidentiality
We will do everything we can to protect your privacy. Your identity will not be revealed in any publication resulting from this study.

Voluntary participation
Your participation in this research study is voluntary. You may choose not to participate and you may withdraw your consent to participate any time. You will not be penalized in any way should you decide not you participate or to withdraw from this study.

CONSENT

I have read this consent form and have been given the opportunity to ask questions. I give my consent to participate in this study.

Participant's signature _____ Date: _____

A copy of this consent form should be given to the participant.

QUESTIONNAIRE

Sociodemographic factors

1. Name of respondent _____

2. Father's name _____

3. Contact number _____

4. Age of the baby (months) _____

5. Gender: Male Female

6. Child's gestational age > 37 weeks < 37weeks

7. Mother's education _____

8. Father's education _____

9. Monthly income of family _____

10. Number of under-five siblings _____

11. Household member number _____

12. Exclusive breastfeeding: Yes No

13. Age of starting of semi solid diet _____

Anthropometric Measurements

14. Weight (kg) _____

15. Height (cm) _____

16. MUAC (cm) _____

17. Weight-for-height Z-score _____

18. Weight-for-age Z-score _____

19. Height-for-age Z-score _____

Group:

20. SAM _____ Normal _____

Denver Developmental Screening Tool II

21. Personal or social development:	Delayed	Normal
22. Fine motor development:	Delayed	Normal
23. Language development:	Delayed	Normal
24. Gross motor development:	Delayed	Normal
25. Global development:	Delayed	Normal

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	5-6, 8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6-8
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.