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ANTENATAL CARE SERVICES AND ITS IMPLICATIONS FOR VITAL AND HEALTH OUTCOMES OF CHILDREN

Evidence from 171 Surveys in 69 Low- and Middle-Income Countries

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ABSTRACT

Objectives: Antenatal care (ANC) is an essential part of basic primary health care and its provision has expanded worldwide. There is limited evidence of large-scale cross-country studies on impact of ANC offered to pregnant women on child health outcomes. We investigate the association of ANC in low- and middle-income countries on short- and long-term mortality and nutritional child outcomes.

Setting: Nationally representative health and welfare data from 171 Demographic and Health Surveys (DHS) conducted between Jan 1, 1990, and Dec 31, 2013 from 69 low- and middle-income countries for women of reproductive age (15-49), their children, and respective household.

Participants: Total sample: 1,044,450 children. Observations were lost due to missing data on outcome/exposure variables or covariates. Analytical sample: 751,871 for neonatal mortality, 574,017 for infant mortality, 399,769 for low birthweight, 501,251 for stunting, 512,196 for underweight. Only information from last-born live births considered.

Main Outcomes and Measures: Neonatal and infant mortality, low birth-weight, stunting (low height-for-age) and underweight (low weight-for-age).

Results: Prevalence of neonatal mortality higher among women not receiving any ANC check-up (3.06%) compared to attending at least one check-up (1.67%). For infant mortality the respective numbers are 4.20% and 2.21%. Women not attending ANC on average lower educated and poorer than women attending at least one ANC check-up.

ANC associated with 0.97 pp lower probability of neonatal mortality (P<.001), 1.05 pp lower probability of infant mortality (P<.001), 3.54 pp lower probability of low birthweight (P<.004), 4.29 pp lower probability of stunting (P<.003), 3.31 pp lower probability of underweight (P<.002).

Conclusions: Currently existing and accessed ANC services in low- and middle-income countries are directly associated with improved birth outcomes and longer-term reductions of child mortality and malnourishment. This emphasizes the importance of ANC within the continuum of maternal/child health care. Quality and quantity of ANC services associated with further improvements of short- and long-term vital and nutritional outcomes.

STRENGTHS AND LIMITATIONS

*** First study on the association of antenatal care with child health and vital outcomes that for all low- and middle-income countries for which high quality and comparable data are available**

*** The analysis does not allow a causal interpretation of the results.**

INTRODUCTION

Despite strong international efforts to expand the worldwide coverage of basic primary health services for women, pregnancy and childbirth still represent a high-risk period for mother and child, especially in low- and middle-income countries. Nearly three million babies die every year during their first month of life. Especially in low- and middle-income countries many of those deaths and morbidities are due to easily preventable causes. Undetected infections during pregnancy, like malaria, syphilis, tuberculosis, tetanus, or HIV/AIDS, as well as high blood pressure, diabetes, and other pre-existing health conditions often complicate or aggravate a pregnancy and pose significant risk for mother and child. Antenatal care (ANC) – the services offered to mother and unborn child during pregnancy – is an essential part of the basic primary health care offering a mosaic of services that can prevent, detect, and treat such risk factors early on in the pregnancy. The detection of high-risk pregnancies through the analysis of socioeconomic, medical and obstetrical factors represents a key element of antenatal care. It is also often used as a platform for additional interventions that have been shown to positively influence the maternal and child health status, like immunization and nutrition programs, breastfeeding counselling, or to educate women about the possibilities of family planning and birth spacing.[1-5] Additionally, antenatal care programs are used to provide care and information that is not directly related to pregnancy but can reduce possible maternal risk factors, like promoting healthy lifestyles, to tackle malnutrition or inform about gender-based violence. Hence, antenatal care is a potentially important determinant in reducing maternal and child morbidity and mortality.[6-13] Within the last decades, the provision of antenatal care services has increased worldwide and during 2006-2013 the antenatal care coverage defined as at least one antenatal care visit with a skilled provider was around 75% in low- and lower-middle income countries.[14,15] To our knowledge, there exists no global study for all low- and middle-income countries, which analyses the association of existing antenatal care services that are offered to pregnant women in low- and middle-income countries on child health outcomes.

Numerous studies have helped to develop an internationally accepted set of so-called, essential antenatal care services' by evaluating the effects of single interventions, like tetanus and malaria prevention programs, on maternal and neonatal health[16-18] or by studying the optimal number and content of antenatal care visits.[19,20] But the de facto offered and utilized set of antenatal care services

can deviate greatly from those recommended interventions across as well as within countries. A couple of studies evaluate the relationship between the utilization of antenatal care services and perinatal outcomes in individual low- and middle-income countries. The majority have shown positive effects of antenatal care on newborn mortality, the occurrence of stillbirth and pre-term labour, and low birthweight.[21-26] However, they exclusively focus on single countries, are often conducted at the clinic level, and have small sample sizes. This limits their external validity. We identified only one study that focuses on a larger regional sample. Conde-Agudelo et al. (2000) studied 837,232 births in Latin America between 1985 and 1997. [27] One major risk factor associated with fetal death was the lack of antenatal care. We could not find a study that took into account possible long-term effects of the utilization of antenatal care services on children's nutritional and vital status.

With up to 171 Demographic and Health Surveys (DHS) from up to 69 low- and middle-income countries we use the most comprehensive data for low- and middle-income countries in the world that currently exist. Specifically, we investigate whether the attendance of mothers at antenatal care services was associated with improved short- and long-term survival rates or reductions in the prevalence of low birthweight, stunting and underweight in their children.

METHODS

Data

We used data from the Demographic and Health Surveys (DHS), which are cross-sectional household surveys that use a harmonized questionnaire to facilitate between-country comparisons. The DHS collect nationally representative health and welfare data for women of reproductive age, age 15-49, their children and the respective household.

They have been conducted at different time intervals in 90 low- and middle-income countries since 1985. We included all surveys, which have information for the relevant outcome and explanatory variables. The final sample consists of pooled data from up to 171 surveys in 69 low- and middle-income countries worldwide conducted between Jan 1, 1990, and Dec 31, 2013. The DHS used a multistage stratified sampling, countries were divided into regions, within which populations were

stratified by area of residence and from which a random sample was taken according to the most recent population census. Those are the primary sampling units (clusters with on average 250 households), which are equally likely to be selected to the proportion the specific cluster's population contributed to the total population. At a second stage, after a complete listing of all households within the cluster, an average of 20-30 households was randomly selected by equal probability. Sampling weights in order to calculate nationally representative statistics are provided by DHS.

For each live birth the women were among other things asked about date of birth, birthweight, vital status at the time of the interview, and either current age or age of death of the child. Furthermore, the DHS collected information on the height and weight of the children born during the last five years. For each last-born live birth there is information on the attendance rates and quality of antenatal care visits during the last pregnancy that led to a live birth. Considering the on-going debates on the importance of the quality and number of antenatal care visits[20,28-30] we specified three different main explanatory variables, including the mere attendance of antenatal care (irrespective of number and quality of the visits), the provision of service by a skilled attendant, and the attendance of at least four ANC visits as recommended by the WHO. Antenatal care visits with a doctor, midwife, nurse, auxiliary midwife, obstetrician, health professional, or trained (traditional) birth attendant, we considered as skilled antenatal care services. Whereas antenatal care with a traditional birth attendant, relatives, any other person or none of the mentioned was classified as unskilled antenatal care.

Outcomes

We analysed the data for short- and long-term vital outcomes and low birthweight of all last-born live births as well as stunting and underweight for the last-born children aged 0-59 months at the time of the interview. Mortality outcomes were neonatal death, defined as death within the first month of life and infant death, defined as death after the first month but within the first year of life. Nutritional outcomes were low birthweight, stunting and underweight. We used the WHO classification that defines low birthweight as a birthweight below 2,500g at birth. Following WHO and UNICEF suggestions, we only included biologically plausible birthweights from 500 – 5999g. To calculate stunting and underweight, we used anthropometric data defined by WHO standards and

classifications. Comparing the child's height and weight to those of a well-nourished reference population of the same age and sex, allows us to calculate the z-scores of height-for-age and weight-for-age. Stunting is defined by a height-for-age z-score of less than -2 and underweight is defined by a weight-for-age z-score of less than -2. Biologically implausible values of the z-scores were excluded following WHO guidelines.

Statistical Analysis

We used linear probability regression models to investigate the association between antenatal care services and short- and longer-term vital and health outcomes of children. We adjusted the regressions for confounding factors and controlled for PSU fixed effects. Standard errors were clustered at the PSU level. They capture characteristics of local enumeration areas that are common to all respondents from that area. We used sex, birth order, birth spacing, birth month, and whether the child was a multiple birth; the mother's age at birth, education, work status, relation to the household head, and her marital status; and household wealth quintile as covariates. The wealth quintile variable is based on the ownership of household assets and indicates the household's wealth relative to other households within the respective country in that survey. Additionally, by including variables indicating place of delivery, mode of delivery (vaginal or caesarean), status of tetanus injection of mother before birth, and if she breastfed at least one month after birth (only applicable for long-term outcomes), we inspected possible mediator variables meaning that the uptake of antenatal care services might starkly influence those variables, which themselves might affect the outcome variables.

Using Stata (version 14.0) for all statistical analyses, we also took into account the stratified survey design by using the Stata svy command. We used sampling weights provided by DHS in all our regressions.

RESULTS

The total sample included observations for 1,044,450 children. Observations were lost due to missing data on outcome variables, missing data on the ANC variables (including the dummies indicating the mere attendance of ANC visits, the attendance at skilled providers, and whether at least four visits

were accomplished during the pregnancy) or missing data on covariates. The final analytical sample is 751,871 for neonatal mortality, 399,769 for low birthweight, 574,017 for infant mortality, 501,251 for stunting and 512,196 for underweight (see Figure 1).

The prevalence of newborn death was higher among women that did not receive any antenatal care check-up (3.06 percent) compared to those attending at least one check-up (1.67 percent). For infant mortality the respective numbers are 4.20 percent and 2.21 percent. Prevalence of all outcome variables was higher among women not attending any antenatal care visit than those attending at least one antenatal check-up (Table 1). Pregnant women that did not attend antenatal care visits were on average lower educated and poorer than those women that attended at least one ANC check-up (see Table A1 in the appendix).

In Table 2 we report the association between antenatal care take-up and short- and long-term mortality outcomes. For each outcome, we show the results from five different specifications where PSU fixed effects are included in all five. The first column shows the mere association between the attendance of at least one ANC visit without controlling for any covariates. The second column shows the association adjusted for control variables and the third column shows the association that in addition to control variables is also adjusted for potential transmission channels of antenatal care (place of delivery, mode of delivery, status of tetanus toxoid (TT) injection of mother before birth, and for the long-term outcomes we also include if the mother breastfed at least for one month after birth). The fourth column reports the coefficients while adding whether the mother has attended her antenatal care visits at a skilled provider and if she received at least four visits before the delivery. The last column includes potential transmission channels. We will focus on the second and fourth specification adjusted for control variables and only refer to the other three specifications for comparison purposes.

Women attending at least one antenatal care visit have a 0.98 percentage points reduced probability of their newborn dying within the first month after birth and a 1.05 percentage points lower probability of experiencing death of their child within the first year of life. While the quality of the provider is not significantly related to neonatal mortality, the quantity is. Having at least four ANC

visits is associated with 0.54 percentage points fewer neonatal deaths. The association between antenatal care check-ups and infant mortality, seems to be driven by the quality and quantity of prenatal visits. Once controlling for the quality and number of visits, the coefficient for at least one ANC visit is not statistically significant anymore. Going to a skilled provider is associated with 0.69 percentage points fewer infant deaths. Additionally, having at least four ANC check-ups, is associated with 0.48 percentage points fewer infant deaths.

The DHS dataset also provides information on several variables that are well established in the literature to impact mortality and morbidity outcomes of children and that simultaneously are potentially influenced by ANC attendance. When controlling for these potential transmission channels of antenatal care services, it can be seen that some of the ANC coefficients are somewhat attenuated when controlling for these additional variables but not by much. Results for all covariates are provided in the appendix (Table A2).

In Table 3 we report the association between antenatal care and short- and long-term nutritional outcomes of the child. If the mother chooses to have at least one ANC visit, this is associated with a 3.54 percentage points reduced probability of giving birth to a low birthweight baby. Stunting and underweight outcomes are reduced by 4.29 and 3.31 percentage points respectively. The association between antenatal care check-ups and low birthweight as well as underweight, seem also to be driven by the quality and quantity of prenatal visits. Once controlling for the quality and number of visits, the coefficient for at least one ANC visit looses its significance. Attendance at a skilled provider reduces the probability of having a low birthweight baby by 1.37 percentage points and for underweight by 2.18 percentage points. Additionally having at least four ANC check-ups, reduces the outcomes by 2.76 percentage points and 2.06 percentage points respectively. In case of stunting the coefficient indicating at least one ANC visit remains significant when adding quality and quantity indicators. Going to a skilled provider is associated with 2.17 percentage points reduced stunting probability and attending at least four ANC check-ups reduces stunting probability by 1.57 percentage points.

Adding potential transmission channels of antenatal care services to the regression slightly attenuates the three ANC coefficients (more so in the case of LBW). Results for all covariates are provided in the appendix (Table A2).

DISCUSSION

Most existing evidence on the effect of antenatal care on child health is based on data from high-income countries and their conclusions are not easily transferable to low- and middle-income settings. The existing studies for low- and middle-income countries often focus on individual countries. Furthermore, the studied effects of antenatal care have been limited to direct short-term maternal and child delivery outcomes. This is the first large-scale cross-country study for all low-and middle-income countries with availability of comparable data for ANC, which systematically investigates the association of ANC with short- and long-term mortality and nutritional child outcomes.

Using child vital data and child anthropometry from up to 171 surveys in 69 low- and middle-income countries we have shown that antenatal care is associated with reductions in neonatal and infant mortality, low birthweight, stunting and underweight. This association can be seen for all outcomes in almost all world regions though it is especially strong in Latin America and Caribbean, Sub-Saharan Africa, and South and Southeast Asia (which constitute about 90% of our sample). Receiving prenatal care by skilled providers is significantly associated with prevalence reductions of all outcome variables (except for neonatal mortality) and hence, plays an important role in the provision of ANC services. The same is true for the quantity of antenatal care visits during pregnancy. Receiving at least four ANC check-ups, improves the outcomes of all short- and long-term child health indicators. The magnitude of the association is quantitatively important, as it varies around -0.98 and -4.29 percentage points. Currently, 47 children out of 1000 livebirths die in the developing world before their fifth birthday.[31]

Many pregnant women in low- and middle-income countries have no access or do not attend ANC services regularly enough (4+ visits) or at skilled providers.[14,32] According to our results, improving the coverage and uptake of antenatal care services could be an important tool to improve short- and even long-term mortality and nutritional outcomes of children.

There are a couple of self-selection issues and limitations, which we have attempted to address. For instance, we controlled for mother's education and household wealth, since more educated or more affluent mothers might be more likely to seek antenatal care and at the same time have a better overall health status. Similarly, we adjusted for PSU fixed effects to control for community characteristics, overall health status in the region and the local availability and quality of health care services as well as other characteristics that are common to the local area. However, there are a few maternal characteristics, which we did not observe and therefore were not able to control for. For instance, if pregnant women feel that there could be something wrong, they might be more likely to seek antenatal care. Similarly, if women had negative birth outcomes in the past, they might also be more likely to seek antenatal care to avoid the repetition of the negative birth outcome. Both cases would downward bias our estimates, and the true association would be even stronger than the association, which we found in our analysis. It is important to point out again that we are only including the outcomes of livebirths. The attendance at antenatal care services might lead to better survival chances of those babies that would have otherwise died before birth. This might impose a downward bias on our estimates. However, there are also potential selection issues, which could bias the results in the other direction. For instance it is unclear how women would behave in case of an unwanted pregnancy, they might be less likely to seek antenatal care and have worse overall health behaviour compared to women in planned pregnancies. In a robustness check we controlled for an indicator variable if the pregnancy was wanted and this did not change the results.

In summary, our study provides evidence for the potential importance of antenatal care for improving child health and vital outcomes in low- and middle-income countries.

A. CONTRIBUTOR SHIP STATEMENT

JK and SV conceptualized the study and developed the analytical strategy. JK wrote the first draft of the paper, conducted the statistical analysis and interpreted the data. SV contributed to the interpretation of the results and critically revised it.

B. COMPETING INTERESTS

The authors have read and understood BMJ policy on declaration of interests and declare that they have no competing interests.

C. FUNDING

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D. DATA SHARING STATEMENT

This study used data that was collected by the Demographic and Health Surveys Program (www.dhsprogram.com), under a contract from the U.S. Agency for International Development.

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Table 1: Descriptive Statistics

Outcome variable	Mother attended at leat 1 ANC visit; % (n=615621)	Mother did not attend ANC visit, % (n=136250)
Neonatal Mortality	1.67	3.06*
Infant Mortality	2.21	4.20*
Low Birthweight	9.69	14.24*
Stunting	31.37	47.11*
Underweight	15.72	30.73*
n values denote the number of observations in the neonatal mortality sample. * Proportions in the two groups were significantly different from each other, p ≤ 0.05 (t test).		

Table 2: Associations between antenatal care visits and mortality outcomes

Neonatal Mortality					
	(1)	**(2)**	**(3)**	**(4)**	**(5)**
at least 1 ANC visit	-0.0101*** [0.001]	-0.00977*** [0.001]	-0.00468*** [0.001]	-0.00567*** [0.002]	-0.00376** [0.002]
skilled ANC provider				-0.00162 [0.002]	0.00151 [0.002]
at least 4 ANC visits				-0.00537*** [0.001]	-0.00532*** [0.001]
facility delivery			0.00193*** [0.001]		0.00244*** [0.001]
mother had TT injct			-0.00822*** [0.001]		-0.00792*** [0.001]
delivery by C-section			0.0102*** [0.001]		0.0103*** [0.001]
N	751871	751871	688612	751871	688612
Infant Mortality					
	(1)	**(2)**	**(3)**	**(4)**	**(5)**
at least 1 ANC visit	-0.0126*** [0.001]	-0.0105*** [0.001]	-0.00614*** [0.001]	-0.00160 [0.003]	-0.000395 [0.003]
skilled ANC provider				-0.00690*** [0.002]	-0.00423* [0.002]
at least 4 ANC visits				-0.00475*** [0.001]	-0.00400*** [0.001]
facility delivery			-0.00185** [0.001]		-0.00138* [0.001]
mother had TT injct			-0.00541*** [0.001]		-0.00503*** [0.001]
delivery by C-section			0.00127 [0.001]		0.00140* [0.001]
child was breastfed			-0.0498*** [0.002]		-0.0497*** [0.002]
N	574017	574017	522419	574017	522419
Controls	**no**	**yes**	**yes**	**yes**	**yes**
All regressions include PSU fixed effects. ***, ** and * denote significance at the 1%, 5%, and 10% levels, respectively. Std. Errors in square brackets and are clustered at PSU level. Control variables include: Mother's age, marital status and educational achievement, whether she heads the HH, child's sex and birth order and spacing, month of birth, whether it was a multiple birth and HH wealth quintile.					

Table 3: Associations between antenatal care visits and nutritional outcomes

Low Birthweight					
	(1)	**(2)**	**(3)**	**(4)**	**(5)**
at least 1 ANC visit	-0.0403*** [0.004]	-0.0354*** [0.004]	-0.0323*** [0.004]	-0.00249 [0.009]	0.00166 [0.009]
skilled ANC provider				-0.0137* [0.008]	-0.0158* [0.008]
at least 4 ANC visits				-0.0276*** [0.002]	-0.0277*** [0.002]
facility delivery			0.00181 [0.002]		0.00349 [0.002]
mother had TT injct			-0.00646*** [0.002]		-0.00457** [0.002]
delivery by C-section			0.0204*** [0.002]		0.0209*** [0.002]
N	399769	399769	367490	399769	367490
Stunting					
	(1)	**(2)**	**(3)**	**(4)**	**(5)**
at least 1 ANC visit	-0.0693*** [0.003]	-0.0429*** [0.003]	-0.0375*** [0.003]	-0.0145** [0.007]	-0.0155** [0.008]
skilled ANC provider				-0.0217*** [0.007]	-0.0172** [0.007]
at least 4 ANC visits				-0.0157*** [0.002]	-0.0128*** [0.002]
facility delivery			-0.0363*** [0.002]		-0.0347*** [0.002]
mother had TT injection			0.00185 [0.002]		0.00277 [0.002]
delivery by C-section			0.00441* [0.003]		0.00483* [0.003]
child was breastfed			-0.0282*** [0.005]		-0.0282*** [0.005]
child ever got vaccine			0.0544*** [0.004]		0.0550*** [0.004]
N	501251	501251	457622	501251	457622
Underweight					
	(1)	**(2)**	**(3)**	**(4)**	**(5)**
at least 1 ANC visit	-0.0505*** [0.002]	-0.0331*** [0.002]	-0.0226*** [0.002]	-0.00225 [0.006]	-0.00224 [0.007]
skilled ANC provider				-0.0218*** [0.006]	-0.0136** [0.006]
at least 4 ANC visits				-0.0206*** [0.002]	-0.0168*** [0.002]
facility delivery			-0.0252*** [0.002]		-0.0232*** [0.002]
mother had TT injct			-0.00443** [0.002]		-0.00338* [0.002]
delivery by C-section			-0.00569*** [0.002]		-0.00515*** [[0.002]
child was breastfed			-0.0164*** [0.004]		-0.0163*** [0.004]

child ever got vaccine			-0.00336 [0.003]		-0.00269 [0.003]
N	512196	512196	467001	512196	467001
Controls	**no**	**yes**	**yes**	**yes**	**yes**
All regressions include PSU fixed effects. ***, ** and * denote significance at the 1%, 5%, and 10% levels, respectively. Std. Errors in square brackets and are clustered at PSU level. Control variables include: Mother's age, marital status and educational achievement, whether she heads the HH, child's sex and birth order and spacing, month of birth, whether it was a multiple birth and HH wealth quintile.					

Table A1: Covariates across exposure category

Covariate	Mother attended at leat 1 ANC visit; % (n=615621)	Mother did not attend ANC visit, % (n=136250)
Maternal education		
None	45.40	82.97*
Primary or incompl. Secondary	33.91	13.33*
Secondary or higher	20.69	3.70*
Maternal age at birth		
≤ 17 years	3.51	4.90*
17 - 19 years	12.87	12.51*
20 - 24 years	28.23	25.15*
25 - 29 years	24.53	23.08*
30 years or older	30.86	34.35*
Mother is working	57.21	50.97*
Mother is HH Head	9.13	7.24*
Mother is married	72.25	85.79*
Child is female	48.71	48.74
Multiple birth	0.88	0.98*
Birth order		
First child	31.24	19.37*
Second child	21.60	16.19*
Third child	15.57	14.58*
Fourth child	10.41	12.64*
Fifth or later born child	21.18	37.23*
Birth spacing ≤ 18 mths	3.55	5.57*
Wealth quintiles		
First quintile	15.16	32.46*
Second quintile	17.54	26.84*
Third quintile	19.89	20.42
Fourth quintile	22.32	13.85*
Fifth quintile	25.10	6.42*

N values denote the number of observations in the neonatal mortality sample. Values were popoulation weighted. * Proportions in the two groups were significantly different from each other, $p \leq 0.05$ (t test).

Table A2: Associations between the exposure variables and full set of control variables

	Neonatal Mortality	Infant Mortality	Low Birthweight	Stunting	Underweight
Maternal education *[reference: no education]*					
Primary or incompl. Secondary	-0.00247*** [0.001]	-0.00544*** [0.001]	-0.0183*** [0.002]	-0.0448*** [0.002]	-0.0363*** [0.002]
Secondary or higher	-0.00516*** [0.001]	-0.00916*** [0.001]	-0.0346*** [0.002]	-0.0778*** [0.003]	-0.0453*** [0.002]
Maternal age at birth *[reference: ≤*					
17 - 19 years	-0.00504*** [0.001]	-0.00684*** [0.002]	-0.00847** [0.004]	-0.0503*** [0.005]	-0.0352*** [0.004]
20 - 24 years	-0.00781*** [0.001]	-0.0104*** [0.002]	-0.0211*** [0.004]	-0.0754*** [0.004]	-0.0499*** [0.004]
25 - 29 years	-0.00697*** [0.001]	-0.00990*** [0.002]	-0.0214*** [0.004]	-0.101*** [0.005]	-0.0576*** [0.004]
30 years or older	-0.000944 [0.001]	-0.00903*** [0.002]	-0.00921** [0.004]	-0.118*** [0.005]	-0.0597*** [0.004]
Mother is working	0.00333*** [0.000]	0.00144** [0.001]	-0.000679 [0.001]	0.0169*** [0.002]	0.00674*** [0.002]
Mother is HH Head	-0.000707 [0.001]	-0.000768 [0.001]	-0.000502 [0.002]	0.00555** [0.003]	-0.00265 [0.002]
Mother is married	-0.00172*** [0.001]	-0.00607*** [0.001]	-0.00955*** [0.002]	-0.00749**** [0.002]	-0.00868*** [0.002]
Child is female	-0.00453*** [0.000]	-0.00191*** [0.001]	0.0200*** [0.001]	-0.0394*** [0.002]	-0.0223*** [0.001]
Multiple birth	0.100*** [0.004]	0.0649**** [0.005]	0.384*** [0.010]	0.144*** [0.009]	0.146*** [0.008]
Birth order *[reference: First born child]*					
Second child	-0.00888*** [0.001]	-0.00455*** [0.001]	-0.0275*** [0.002]	0.0290*** [0.002]	0.00553*** [0.002]
Third child	-0.0104*** [0.001]	-0.00487*** [0.001]	-0.0324*** [0.002]	0.0462*** [0.003]	0.0149*** [0.002]
Fourth child	-0.0113*** [0.001]	-0.00538*** [0.001]	-0.0365*** [0.003]	0.0582*** [0.003]	0.0202*** [0.003]
Fifth or later born child	-0.0108*** [0.001]	-0.00353*** [0.001]	-0.0396*** [0.003]	0.0837*** [0.003]	0.0294*** [0.003]
Birth spacing ≤ 18 months	0.0199*** [0.001]	0.0228*** [0.002]	0.0228*** [0.004]	0.0491*** [0.004]	0.0308*** [0.003]
Wealth quintiles *[reference: poorest 20%]*					
Second quintile	-0.000750 [0.001]	-0.00202** [0.001]	-0.00730*** [0.002]	-0.0173*** [0.003]	-0.0123*** [0.002]
Third quintile	-0.0000752 [0.001]	-0.00254** [0.001]	-0.0123*** [0.003]	-0.0367*** [0.003]	-0.0308*** [0.002]

Fourth quintile	-0.0000543 [0.001]	-0.00561*** [0.001]	-0.0173*** [0.003]	-0.0586*** [0.003]	-0.0501*** [0.003]
Fifth quintile	-0.00113 [0.001]	-0.00653*** [0.001]	-0.0216*** [0.003]	-0.0988*** [0.003]	-0.0766*** [0.003]
Month of birth	0.00000989 [0.000]	-0.0000732 [0.000]	-0.000215 [0.000]	-0.00375*** [0.000]	-0.00294*** [0.000]
N	**751871**	**574017**	**399769**	**501251**	**512196**

Results are from the main results regressions (4). ***, ** and * denote significance at the 1%, 5%, and 10% levels, respectively. Std. Errors in square brackets and are clustered at PSU level.

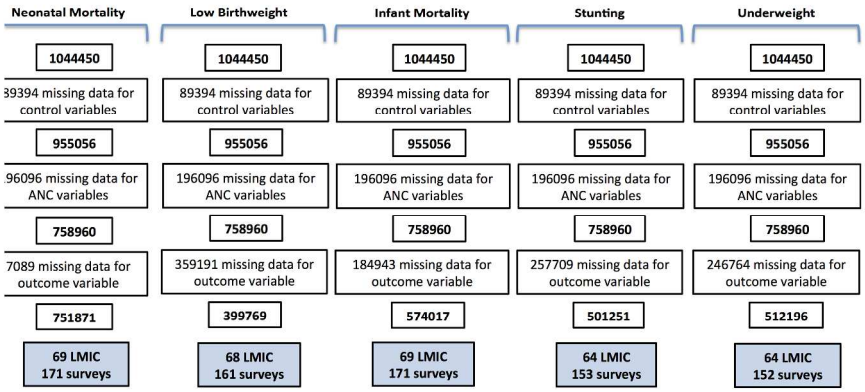

Figure 1: Sample deduction

297x209mm (300 x 300 DPI)

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	2-3
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	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
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	6
		(*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	6-7
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*
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	6,8
		(*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	8
		(*e*) Describe any sensitivity analyses	

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
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9 (table A1)
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
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	*9*
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
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	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	
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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Antenatal Care Services and its Implications for Vital and Health Outcomes of Children: Evidence from 193 Surveys in 69 Low- and Middle-Income Countries

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ANTENATAL CARE SERVICES AND ITS IMPLICATIONS FOR VITAL AND HEALTH OUTCOMES OF CHILDREN

Evidence from 193 Surveys in 69 Low- and Middle-Income Countries

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ABSTRACT

Objectives: Antenatal care (ANC) is an essential part of primary health care and its provision has expanded worldwide. There is limited evidence of large-scale cross-country studies on the impact of ANC offered to pregnant women on child health outcomes. We investigate the association of ANC in low- and middle-income countries on short- and long-term mortality and nutritional child outcomes.

Setting: We used nationally representative health and welfare data from 193 Demographic and Health Surveys (DHS) conducted between 1990 and 2013 from 69 low- and middle-income countries for women of reproductive age (15-49), their children, and respective household.

Participants: The analytical sample consisted of 752,635 observations for neonatal mortality, 574,675 observations for infant mortality, 400,426 observations for low birthweight, 501,484 observations for stunting, 512,424 observations for underweight.

Main Outcomes and Measures: Outcome variables are neonatal and infant mortality, low birthweight, stunting and underweight.

Results: At least one antenatal care visit was associated with a 1.04 percentage points reduced probability of neonatal mortality and a 1.07 percentage points lower probability of infant mortality. Having at least four ANC visits and at having at least once seen a skilled provider reduced the probability by an additional 0.56 and 0.42 percentage points respectively. At least one ANC visit is associated with a 3.82 percentage points reduced probability of giving birth to a low birthweight and a 4.11 and 3.26 percentage points reduced stunting and underweight probability. Having at least four ANC visits and at having at least once seen a skilled provider reduced the probability by an additional 2.83, 1.41 and 1.90 percentage points respectively.

Conclusions: The currently existing and accessed ANC services in low- and middle-income countries are directly associated with improved birth outcomes and longer-term reductions of child mortality and malnourishment.

STRENGTHS AND LIMITATIONS

*** First study on the association of antenatal care with child health and vital outcomes for all low- and middle-income countries for which high quality and comparable data are available.**

* First study investigating possible long-term effects of the utilization of ANC on children's nutritional and vital status.

* The study focuses on the association between the antenatal care services effectively available and accessible to women in low- and middle-income countries and hence, generates knowledge on the current status quo and effect of the ANC services on child health.

* The analysis does not allow a causal interpretation of the results.

* Data availability limits the investigation of the association of more disaggregated quality indicators of ANC with the outcome variables.

INTRODUCTION

Despite strong international efforts to expand the worldwide coverage of basic primary health services for women, pregnancy and childbirth still represent a high-risk period for mother and child, especially in low- and middle-income countries. As part of the Sustainable Development Goal 3, reductions in maternal and early child mortality are remaining high on the global development policy agenda.[1] Still nearly three million babies die every year during their first month of life while especially in low- and middle-income countries many of those deaths and morbidities are due to easily preventable causes.[2,3] Undetected infections during pregnancy, like malaria, syphilis, tuberculosis, tetanus, or HIV/AIDS, as well as high blood pressure, diabetes, and other pre-existing health conditions often complicate or aggravate a pregnancy and pose significant risk for mother and child. Antenatal care (ANC) – the services offered to mother and unborn child during pregnancy – is an essential part of the basic primary health care offering a mosaic of services that can prevent, detect, and treat such risk factors early on in the pregnancy. The detection of high-risk pregnancies through the analysis of socioeconomic, medical and obstetrical factors represents a key element of antenatal care. It is also often used as a platform for additional interventions that have been shown to positively influence the maternal and child health status, like immunization and nutrition programs, breastfeeding counselling, or to educate women about the possibilities of family planning and birth spacing.[4-13] Additionally, antenatal care programs are used to provide care and information that is not directly related to pregnancy but can reduce possible maternal risk factors, like promoting healthy lifestyles, to tackle malnutrition or inform about gender-based violence.

Hence, antenatal care is a potentially important determinant in reducing maternal and child morbidity and mortality.[14-22] Within the last decades, the provision of antenatal care services has increased worldwide and during 2010-2015 the antenatal care coverage defined as the percentage of women aged 15-49 that attended at least one antenatal care visit with a skilled provider was around 85% globally and around 77% in the least developed countries .[23,24] To our knowledge, there exists no global study for all low- and middle-income countries, which analyses the association of existing antenatal care services that are offered to pregnant women in low- and middle-income countries on child health outcomes.

Numerous studies have helped to develop an internationally accepted set of so-called, essential antenatal care services by evaluating the effects of single interventions, like tetanus and malaria prevention programs, on maternal and neonatal health[25-30] or by studying the optimal number and content of antenatal care visits.[31-34] But the de facto offered and utilized set of antenatal care services can deviate greatly from those recommended interventions across as well as within countries. A couple of studies evaluate the relationship between the utilization of antenatal care services and perinatal outcomes in individual low- and middle-income countries. The majority have shown positive effects of antenatal care on newborn mortality, the occurrence of stillbirth and pre-term labour, and low birthweight.[35-43] However, they exclusively focus on single countries, are often conducted at the clinic level, and have small sample sizes. This limits their external validity. We identified only one study that focuses on a larger regional sample. Conde-Agudelo et al. (2000) studied 837,232 births in Latin America between 1985 and 1997. [44] One major risk factor associated with fetal death was the lack of antenatal care. We could not find a study that took into account possible long-term effects of the utilization of antenatal care services on children's nutritional and vital status.

With up to 193 Demographic and Health Surveys (DHS) from up to 69 low- and middle-income countries we use the most comprehensive data for low- and middle-income countries in the world that currently exist. Specifically, we investigate whether the attendance of mothers at antenatal care services was associated with improved short- and long-term survival rates or reductions in the prevalence of low birthweight, stunting and underweight in their children.

METHODS

Data

We used data from the Demographic and Health Surveys (DHS), which are publicly available (http://dhsprogram.com). The DHS are cross-sectional household surveys that use a harmonized questionnaire to facilitate between-country comparisons. The DHS collect nationally representative health and welfare data for women of reproductive age (15-49 years), their children and the respective household.

They have been conducted at different time intervals in 90 low- and middle-income countries since 1985. We included all surveys, which have information for the relevant outcome and explanatory variables. The final sample consists of pooled data from up to 193 surveys in 69 low- and middle-income countries worldwide conducted between Jan 1, 1990, and Dec 31, 2013. The DHS used a multistage stratified sampling, countries were divided into regions, within which populations were stratified by area of residence and from which a random sample was taken according to the most recent population census. Those are the primary sampling units (clusters with on average 250 households), which are equally likely to be selected to the proportion the specific cluster's population contributed to the total population. At a second stage, after a complete listing of all households within the cluster, an average of 20-30 households was randomly selected by equal probability. Sampling weights in order to calculate nationally representative statistics are provided by DHS.

For each live birth within the five (or in some cases three) years previous to the survey the women were among other things asked about date of birth, birthweight, vital status at the time of the interview, and either current age or age at death of the child. Furthermore, the DHS collected information on the height and weight of the children born during the last three or five years.

For each last-born live birth of the previous three or five years there is information on the attendance rates and quality of antenatal care visits during the last pregnancy that led to a live birth. Considering the on-going debates on the importance of the quality and number of antenatal care visits[31,45-48] we specified two different main explanatory variables. Firstly, the mere attendance of antenatal care (a dummy variable indicating whether the woman attended at least one ANC visit during her last pregnancy leading to a live birth) irrespective of the total number of visits and the type of provider. In order to proxy the WHO recommendations regarding prenatal care (at least four visits at a skilled provider[1]), we specified a variable indicating whether the woman saw at least once a skilled provider during her at least four ANC visits. Unfortunately, we were unable to identify whether all ANC visits were provided by a skilled professional. Antenatal care visits to a doctor, midwife, nurse, auxiliary midwife, obstetrician, health professional, or trained (traditional) birth attendant, we considered as

[1] In 2016 the WHO updated their recommendations to at least eight prenatal care visits at skilled providers[49].

skilled antenatal care services. Whereas antenatal care with a traditional birth attendant, relatives, any other person or none of the mentioned was classified as unskilled antenatal care.

Outcomes

We analysed the data for short- and long-term vital outcomes and low birthweight of all last-born live births as well as stunting and underweight for the last-born children aged 0-59 (in some surveys 0-36) months at the time of the interview. Hence, each woman is represented only once in the dataset with the information of her last born child (in case of a live birth). Mortality outcomes were neonatal death, defined as death of a live birth within the first month of life and infant death, defined as death after the first month but within the first year of life. The latter excludes neonatal deaths and is restricted to children that aged at least one year. Nutritional outcomes were low birthweight, stunting and underweight. We used the WHO classification that defines low birthweight as a birthweight below 2,500g at birth. Following WHO and UNICEF suggestions, we only included biologically plausible birthweights from 500 – 5999g. To calculate stunting and underweight, we used anthropometric data defined by WHO standards and classifications (using the Stata package 'igrowup_stata'). Comparing the child's height and weight to those of a well-nourished reference population of the same age and sex, allows us to calculate the z-scores of height-for-age and weight-for-age. Stunting is defined by a height-for-age z-score of less than -2 and underweight is defined by a weight-for-age z-score of less than -2. Biologically implausible values of the z-scores were excluded following WHO guidelines.

Statistical Analysis

We used linear probability regression models to investigate the association between antenatal care services and short- and longer-term vital and health outcomes of children. We adjusted the regressions for confounding factors and controlled for PSU fixed effects. The PSU fixed effects are survey specific and herewith, we control for common factors faced by households in the same PSU at one point in time, such as the local availability and quality of health providers, and other local factors. Standard errors were clustered at the PSU level as respondents in the same PSU might experience common shocks. They capture characteristics of

local enumeration areas that are common to all respondents from that area. We used sex, birth order (5 categories: ranging from "First born" to "Fifth or later born" child), birth spacing (5 categories: ranging from "no preceding birth" to "equal or more than 36 months"), birth month, and whether the child was a multiple birth; the mother's age at birth (5 categories: ranging from "below 17" to "equal or above 30" years), education (5 categories: ranging from "no education" to "higher education"), work status, relation to the household head (dummy indicating whether mother is household head), and her marital status; and household wealth quintile as covariates. The wealth quintile variable is constructed by using a principal component analysis and is based on the ownership of household assets (e.g. electricity, television, quality of dwelling) and indicates the household's wealth relative to other households within the respective country in that survey. Additionally, by including variables indicating place of delivery, mode of delivery (vaginal or caesarean), status of tetanus injection of mother before birth, and if she breastfed at least one month after birth (several only applicable for long-term outcomes), we inspected possible mediator variables meaning that the uptake of antenatal care services might starkly influence those variables, which themselves might affect the outcome variables.

Using Stata (version 14.0) for all statistical analyses, we also took into account the stratified survey design by using the Stata svy command. We used sampling weights provided by DHS in all our regressions.

RESULTS

Our initial samples consisted of surveys for which the respective outcome variable and the information on antenatal care visits were collected and consisted of children between 0 and 59 months at the time of the interview and that were permanent members of the respective household. The total sample for neonatal and infant mortality included observations for 1,019,463 children. In some survey rounds data on birthweight and in others on anthropometric measures was not systematically collected. This left us with data of 947,365 children, where information on their birthweight could have potentially been recorded. For stunting this amounted up to 865,959 children and for underweight to 857,908 children.

Observations were lost due to missing data on outcome variables, missing data on the ANC variables (including the dummies indicating the mere attendance of ANC visits, and the attendance of at least 4 ANC visits while the woman at least once saw a skilled provider) or missing data on covariates. The final analytical sample was 752,635 for neonatal mortality, 400,426 for low birthweight, 574,675 for infant mortality, 501,484 for stunting and 512,424 for underweight (see Figure 1 and Table A1).

The prevalence of newborn death was higher among women that did not receive any antenatal care check-up (3.12 percent) compared to those attending at least one check-up (1.67 percent). For infant mortality the respective numbers are 4.23 percent and 2.21 percent. Prevalence of all outcome variables was higher among women not attending any ANC visit than those attending at least one ANC check-up and compared to those that received at least four ANC visits while they at least once have seen a skilled provider (Table 1). Pregnant women that did not attend antenatal care visits were on average less educated and poorer than those women that attended at least one ANC check-up (see Table A2 in the appendix).

In Table 2 we report the association between antenatal care take-up and short- and long-term mortality outcomes. For each outcome, we show the results from three different specifications where PSU fixed effects are included in all three. The first column shows the mere association between the attendance of at least one ANC visit without controlling for any covariates. The second column shows the association adjusted for control variables and the third column reports the coefficients while adding whether the mother has received at least four antenatal care visits during pregnancy while at least having once seen a skilled provider. The interpretation of this additional term follows the logic of an interaction term as it overlaps in its definition with the variable indicating the mere attendance of ANC. Hence, it shows the additional effect if the mother followed more closely the WHO recommendations. In the appendix (Tables A3 & A4) we report the regression results where in addition to control variables we also adjusted for potential transmission channels of antenatal care (place of delivery, mode of delivery, status of tetanus toxoid (TT) injection of mother before birth, and whether the mother breastfed at least for one month after birth). We will focus on the second and third specification adjusted for control variables and only refer to the other specifications for comparison purposes.

Women attending at least one antenatal care visit have a 1.04 percentage points reduced probability of their newborn dying within the first month after birth and a 1.07 percentage points lower probability of experiencing death of their child within the first year of life. Following the WHO recommendations on ANC visits is significantly related to lower mortality outcomes. Compared to the mere attendance of less than four ANC visits (irrespective of the quality of the provider), having at least four ANC visits and at having at least once seen a skilled provider is reducing the probability of neonatal deaths by an additional 0.56 percentage points and is associated with an additional 0.42 percentage points reduction in the probability of infant deaths.

The DHS dataset also provides information on several variables that are well established in the literature to impact mortality and morbidity outcomes of children and that simultaneously are potentially influenced by ANC attendance. When controlling for these potential transmission channels of antenatal care services, it can be seen that the majority of the ANC coefficients are somewhat attenuated when controlling for these additional variables but not by much (Table A3). Results for all covariates are provided in the appendix (Table A5).

In Table 3 we report the association between antenatal care and short- and long-term nutritional outcomes of the child. If the mother attends at least one ANC visit, this is associated with a 3.82 percentage points reduced probability of giving birth to a low birthweight baby. Stunting and underweight outcomes are reduced by 4.11 and 3.26 percentage points respectively. Attendance at a skilled provider during at least one of at least four ANC visits further reduces the probability of having a low birthweight baby by 2.83 percentage points, for stunting by 1.41 percentage points and for underweight by 1.90 percentage points.

Adding potential transmission channels of antenatal care services to the regression slightly attenuates the ANC coefficients in case of low birthweight and underweight (Table A4). Results for all covariates are provided in the appendix (Table A5).

DISCUSSION

Most existing evidence on the effect of antenatal care on child health is based on data from high-income countries and their conclusions are not easily transferable to low- and middle-income

settings. The existing studies for low- and middle-income countries often focus on individual countries. Furthermore, the studied effects of antenatal care have been limited to direct short-term maternal and child delivery outcomes. This is the first large-scale cross-country study for all low-and middle-income countries with availability of comparable data for ANC, which systematically investigates the association of ANC with short- and long-term mortality and nutritional child outcomes.

Using child vital data and child anthropometry from up to 193 surveys in 69 low- and middle-income countries we have shown that antenatal care is associated with reductions in neonatal and infant mortality, low birthweight, stunting and underweight. While we measure average effects across countries and years, we find that this association remains relatively stable across survey rounds (Table A6) and can be seen for all outcomes in almost all world regions (Figures A1 & A2) though it is especially strong in Latin America and Caribbean, Sub-Saharan Africa, and South and Southeast Asia (which constitute about 90% of our sample). Receiving prenatal care by skilled providers and attending at least four ANC visits is significantly associated with additional prevalence reductions of all outcome variables and hence, plays an important role in the provision of ANC services. The magnitude of the association is quantitatively important, as it varies around -1.04 and -4.11 percentage points.

Many pregnant women in low- and middle-income countries have no access or do not attend ANC services regularly enough (4+ visits) or at skilled providers.[23,50,51] According to our results, improving the coverage and uptake of antenatal care services could be an important tool to improve short- and even long-term mortality and nutritional outcomes of children.

There are a couple of self-selection issues and limitations, which we have attempted to address. Unfortunately, we do not have disaggregated information on the type of provider (skilled / unskilled) for each ANC visit. We try to proxy this by including whether the woman has at least once seen a skilled provider during her pregnancy. Further, we controlled for mother's education and household wealth, since more educated or more affluent mothers might be more likely to seek antenatal care and at the same time have a better overall health status. Similarly, we adjusted for PSU fixed effects to control for community characteristics, overall health status in the region and the local availability and quality of health care services as well as other characteristics that are common to the local area.

However, there are a few maternal characteristics, which we did not observe and therefore were not able to control for. For instance, if pregnant women feel that there could be something wrong, they might be more likely to seek antenatal care. Similarly, if women had negative birth outcomes in the past, they might also be more likely to seek antenatal care to avoid the repetition of the negative birth outcome. Both cases would downward bias our estimates, and the true association would be even stronger than the association, which we found in our analysis. It is important to point out again that we are only including the outcomes of livebirths. The attendance at antenatal care services might lead to better survival chances of those babies that would have otherwise died before birth. This might impose a downward bias on our estimates. However, there are also potential selection issues, which could bias the results in the other direction. For instance it is unclear how women would behave in case of an unwanted pregnancy, they might be less likely to seek antenatal care and have worse overall health behaviour compared to women in planned pregnancies. In a robustness check we controlled for an indicator variable if the pregnancy was wanted and this did not change the results. Also we cannot further approximate the quality of care received by the women. As the quality of care will influence the effect of ANC this limits our study. By including PSU level fixed effects we absorb indicators that are similar across this geographical unit and survey. Assuming that the quality of ANC available to women within the same PSU is comparable, we successfully address this data limitation. We also assume that missing data in our sample was not systematically correlated with the true unobserved child health and vital outcomes and the availability and accessibility of ANC services.

In summary, our study provides evidence for the potential importance of antenatal care for improving child health and vital outcomes in low- and middle-income countries and might be an important tool to reach the third Sustainable Development Goal by 2030.

A. CONTRIBUTOR SHIP STATEMENT
JK and SV conceptualized the study, developed the analytical strategy and interpreted the data. JK conducted the statistical analysis and wrote the first draft of the manuscript. SV critically revised the manuscript.

B. COMPETING INTERESTS
The authors have read and understood BMJ policy on declaration of interests and declare that they have no competing interests.

C. FUNDING
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

D. DATA SHARING STATEMENT
This study used data that was collected by the Demographic and Health Surveys Program (www.dhsprogram.com), under a contract from the U.S. Agency for International Development.

E. ETHICAL APPROVAL
Procedures and questionnaires for standard DHS surveys have been approved by the ICF Institutional Review Board (IRB) as well as by the relevant body in each country.
ICF IRB ensures that the survey complies with the U.S. Department of Health and Human Services regulations for the protection of human subjects (45 CFR 46), while the host country IRB ensures that the survey complies with laws and norms of the nation. Oral informed consent for the interview was obtained from respondents by interviewers.

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Table 1: Descriptive Statistics

Outcome variable	Mother attended at least 1 ANC visit; % (n= 616347)	Mother attended at least 4 ANC visits & has seen skilled provider; (n=416350)	Mother did not attend ANC visit, % (n=136288)
Neonatal Mortality	1.67*	1.40*	3.12
Infant Mortality	2.21*	1.81*	4.23
Low Birthweight	9.69*	8.94*	14.35
Stunting	31.35*	27.18*	47.08
Underweight	15.70*	12.02*	30.72
n values denote the number of observations in the neonatal mortality sample. * Proportions to the group "Mother did not attend ANC visit" were significantly different from each other, p ≤ 0.05 (t test).			

Table 2: Associations between antenatal care visits and mortality outcomes

	Neonatal Mortality			Infant Mortality		
	(1)	**(2)**	**(3)**	**(1)**	**(2)**	**(3)**
at least 1 ANC visit	-0.0107*** [0.001]	-0.0104*** [0.001]	-0.00783*** [0.001]	-0.0127*** [0.001]	-0.0107*** [0.001]	-0.00873*** [0.001]
at least 4 ANC visits & skilled ANC provider			-0.00557*** [0.001]			-0.00424*** [0.001]
N	752635	752635	752635	574675	574675	574675
Adjusted for confounding	no	yes	yes	no	yes	yes

All regressions include PSU fixed effects. ***, ** and * denote significance at the 1%, 5%, and 10% levels, respectively. Std. Errors in square brackets and are clustered at PSU level. Control variables include: Mother's age, marital status and educational achievement, whether she heads the HH, child's sex and birth order and spacing, month of birth, whether it was a multiple birth and HH wealth quintile.

Table 3: Associations between antenatal care visits and nutritional outcomes

Low Birthweight	**(1)**	**(2)**	**(3)**
at least 1 ANC visit	-0.0428***	-0.0382***	-0.0187***
	[0.004]	[0.004]	[0.004]
at least 4 ANC visits & skilled ANC provider			-0.0283***
			[0.002]
N	400426	400426	400426
Stunting	**(1)**	**(2)**	**(3)**
at least 1 ANC visit	-0.0677***	-0.0411***	-0.0345***
	[0.003]	[0.003]	[0.003]
at least 4 ANC visits & skilled ANC provider			-0.0141***
			[0.002]
N	501484	501484	501484
Underweight	**(1)**	**(2)**	**(3)**
at least 1 ANC visit	-0.0502***	-0.0326***	-0.0237***
	[0.002]	[0.002]	[0.002]
at least 4 ANC visits & skilled ANC provider			-0.0190***
			[0.002]
N	512424	512424	512424
Adjusted for confounding	no	yes	yes

All regressions include PSU fixed effects. ***, ** and * denote significance at the 1%, 5%, and 10% levels, respectively. Std. Errors in square brackets and are clustered at PSU level. Control variables include: Mother's age, marital status and educational achievement, whether she heads the HH, child's sex and birth order and spacing, month of birth, whether it was a multiple birth and HH wealth quintile.

Figure 1: Sample deduction

Own calculation.

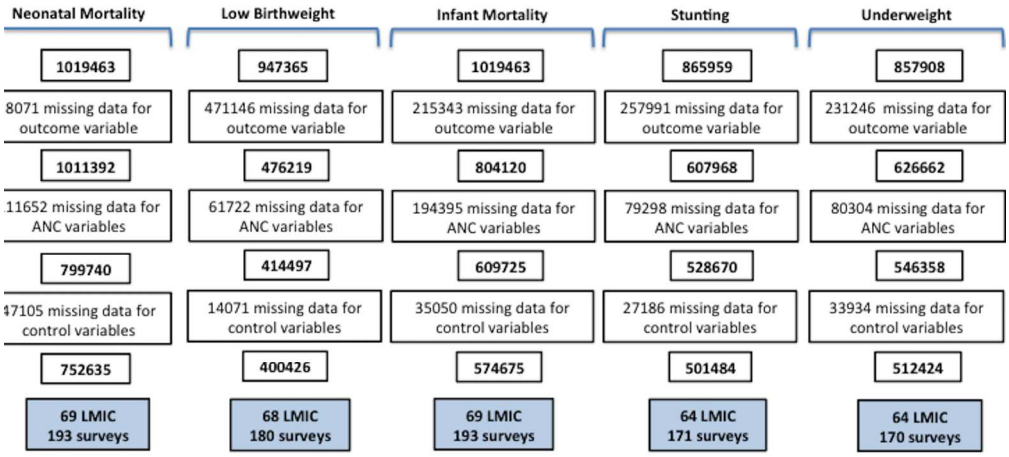

Figure 1

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Table A1: Sample size and surveys across countries

	Phase (Year of survey)	No. obs. (% of total)
Albania	Phase 5 (2008/09)	1,152 (0.15)
Armenia	Phase 4 (2000), Phase 5 (2005), Phase 6 (2010)	2,778 (0.37)
Azerbaijan	Phase 5 (2006)	1,174 (0.16)
Bangladesh	Phase 3 (1993/94, 1996, 1997)*, Phase 4 (1999, 2000)*, Phase 5 (2004, 2007)*, Phase 6 (2011)	23,459 (3.12)
Benin	Phase 3 (1996), Phase 4 (2001)*, Phase 5 (2006), Phase 6 (2011/12)	16,274 (2.16)
Bolivia	Phase 3 (1993/94), Phase 4 (2003/04), Phase 5 (2008)	17,034 (2.26)
Brazil	Phase 2 (1991/92), Phase 3 (1996)	5,339 (0.71)
Burkina Faso	Phase 2 (1992/93), Phase 4 (1998/99, 2003)*, Phase 6 (2010)	15,095 (2.01)
Burundi	Phase 6 (2010/11)	3,224 (0.43)
Cambodia	Phase 4 (2000), Phase 5 (2005/06), Phase 6 (2010/11)	14,645 (1.95)
Cameroon	Phase 2 (1991), Phase 3 (1998), Phase 4 (2004), Phase 6 (2011)	10,344 (1.37)
Central Afr. Republic	Phase 3 (1994/95)	1,451 (0.19)
Chad	Phase 3 (1996/97), Phase 4 (2004)	5,821 (0.77)
Colombia	Phase 3 (1995), Phase 5 (2004, 2005)*, Phase 6 (2009/10)	24,944 (3.31)
Comoros	Phase 3 (1996)	595 (0.08)
Congo (DRC)	Phase 5 (2007)	3,297 (0.44)
Congo (Brazzaville)	Phase 5 (2005), Phase 6 (2011/12)	6,281 (0.83)
Dom. Republic	Phase 2 (1991), Phase 3 (1996), Phase 4 (2002), Phase 5 (2007)	17,845 (2.37)
Egypt	Phase 2 (1992/93), Phase 3 (1995/96), Phase 4 (2000, 2003)*, Phase 5 (2005, 2008)*	37,847 (5.03)
Ethiopia	Phase 4 (2000), Phase 5 (2005), Phase 6 (2011)	14,694 (1.95)
Gabon	Phase 4 (2000/01), Phase 6 (2012)	4,039 (0.54)
Ghana	Phase 3 (1993/94), Phase 4 (1998/99, 2003), Phase 5 (2008)	7,067 (0.94)
Guatemala	Phase 3 (1995), Phase 4 (1998/99)	8,340 (1.11)
Guinea	Phase 4 (1999), Phase 5 (2005), Phase 6 (2012)	8,518 (1.13)
Guyana	Phase 5 (2005, 2009)*	1,004 (0.13)
Haiti	Phase 3 (1994/95), Phase 4 (2000), Phase 5 (2005/06), Phase 6 (2012)	11,927 (1.58)
Honduras	Phase 5 (2005/06), Phase 6 (2011/12)	12,725 (1.69)
India	Phase 4 (1998/99/00), Phase 5 (2005/06)	46,435 (6.17)
Indonesia	Phase 2 (1991), Phase 3 (1994, 1997), Phase 4 (2002/03), Phase 5 (2007), Phase 6 (2012)	64,890 (8.62)
Ivory Coast	Phase 3 (1994), Phase 4 (1998/99), Phase 5 (2005), Phase 6 (2011/12)	8,020 (1.07)
Jordan	Phase 3 (1997), Phase 5 (2007), Phase 6 (2012)	13,205 (1.75)
Kazakhstan	Phase 3 (1995, 1999)*	1,454 (0.19)
Kenya	Phase 2 (1993), Phase 3 (1998), Phase 4 (2003), Phase 5 (2008/09)	9,250 (1.23)
Kyrgyz Republic	Phase 3 (1997), Phase 6 (2012)	2,859 (0.38)
Lesotho	Phase 5 (2004/05), Phase 6 (2009/10)	4,522 (0.60)
Liberia	Phase 5 (2006/07)	2,229 (0.30)
Madagascar	Phase 2 (1992), Phase 3 (1997), Phase 4 (2003/04), Phase 5 (2008/09)	13,746 (1.83)
Malawi	Phase 4 (2000), Phase 5 (2004/05), Phase 6 (2010)	20,486 (2.72)
Maldives	Phase 6 (2009)	2,041 (0.27)

Mali	Phase 3 (1995/96), Phase 4 (2001), Phase 5 (2006)	12,855 (1.71)
Moldova	Phase 5 (2005)	1,153 (0.15)
Morocco	Phase 2 (1992), Phase 5 (2003/04)	6,520 (0.87)
Mozambique	Phase 3 (1997), Phase 4 (2003/04), Phase 6 (2011)	12,008 (1.60)
Namibia	Phase 2 (1992), Phase 4 (2000), Phase 5 (2006/07)	5,961 (0.79)
Nepal	Phase 3 (1996), Phase 4 (2001), Phase 5 (2006), Phase 6 (2011)	11,688 (1.55)
Nicaragua	Phase 3 (1997/98), Phase 4 (2001)	8,658 (1.15)
Nigeria	Phase 2 (1990), Phase 4 (1999, 2003), Phase 5 (2008)	17,896 (2.38)
Niger	Phase 2 (1992), Phase 3 (1998), Phase 5 (2006), Phase 6 (2012)	13,275 (1.76)
Pakistan	Phase 2 (1990/91), Phase 5 (2006/07), Phase 6 (2012/13)	11,236 (1.49)
Paraguay	Phase 2 (1990)	2,421 (0.32)
Peru	Phase 2 (1991/92), Phase 3 (1996), Phase 4 (2000), Phase 5 (2005/06, 2007/08, 2009), Phase 6 (2010/11/12)	57,103 (7.59)
Philippines	Phase 3 (1993, 1998)*, Phase 4 (2003), Phase 5 (2008)	17,568 (2.33)
Rwanda	Phase 2 (1992), Phase 4 (2000), Phase 5 (2005), Phase 6 (2010/11)	15,041 (2.00)
Sao Tome and Principe	Phase 5 (2008/09)	1,072 (0.14)
Senegal	Phase 2 (1992/93), Phase 3 (1997), Phase 4 (2005), Phase 6 (2010/11, 2012/13)*	13,834 (1.84)
Sierra Leone	Phase 5 (2008)	2,202 (0.29)
South Africa	Phase 4 (1998)	3,075 (0.41)
Swaziland	Phase 5 (2006/07)	1,396 (0.19)
Tanzania	Phase 2 (1991/2), Phase 3 (1996), Phase 4 (1999), Phase 5 (2004/5, 2007/8)*, Phase 6 (2009/10)	16,392 (2.18)
Timor-Leste	Phase 6 (2009/10)	3,612 (0.48)
Togo	Phase 4 (1998)	2,196 (0.29)
Turkey	Phase 2 (1993), Phase 4 (1998), Phase 5 (2003/04)	7,980 (1.06)
Uganda	Phase 3 (1995), Phase 4 (2000/01), Phase 5 (2006), Phase 6 (2011)	11,743 (1.56)
Ukraine	Phase 5 (2007)	800 (0.11)
Uzbekistan	Phase 3 (1996)	768 (0.10)
Vietnam	Phase 4 (1997 / 2002)*	2,437 (0.32)
Yemen	Phase 2 (1991/2)	3,369 (0.45)
Zambia	Phase 2 (1992) Phase 3 (1996/97), Phase 4 (2001/02), Phase 5 (2007)	12,572 (1.67)
Zimbabwe	Phase 3 (1994), Phase 4 (1999), Phase 5 (2005/06), Phase 6 (2010/11)	9,754 (1.30)
TOTAL		752,635 (100)

Total numbers and frequencies are based on the neonatal mortality sample. * indicates that more than one survey was conducted within the phase

Table A2: Covariates across exposure category

Covariate	Mother attended at least 1 ANC visit; % (n=616347)	Mother did not attend ANC visit, % (n=136288)
Maternal education		
None	45.41	82.92*
Primary or incompl. Secondary	33.89	13.38*
Secondary or higher	20.70	3.70*
Maternal age at birth		
≤ 17 years	3.51	4.89*
17 - 19 years	12.89	12.52*
20 - 24 years	28.13	25.31*
25 - 29 years	24.58	22.99*
30 years or older	30.88	34.29*
Mother is working	57.25	51.02*
Mother is HH Head	9.13	7.20*
Mother is married	72.24	85.77*
Child is female	48.65	48.88
Multiple birth	0.91	0.10*
Birth order		
First child	31.23	19.41*
Second child	21.60	16.16*
Third child	15.55	14.67*
Fourth child	10.43	12.53*
Fifth or later born child	21.19	37.23*
Birth spacing ≤ 18 mths	3.56	5.58*
Wealth quintiles		
First quintile	15.17	32.49*
Second quintile	17.50	26.81*
Third quintile	19.88	20.39
Fourth quintile	22.30	13.91*
Fifth quintile	25.14	6.40*

N values denote the number of observations in the neonatal mortality sample. Values were population weighted. * Proportions in the two groups were significantly different from each other, p ≤ 0.05 (t test).

Table A3: Associations between mortality outcomes and mediator variables

	Neonatal Mortality		Infant Mortality	
	(1)	(2)	(1)	(2)
at least 1 ANC visit	-0.00520*** [0.001]	-0.00288*** [0.001]	-0.00562*** [0.001]	-0.00416*** [0.001]
at least 4 ANC visits & skilled ANC provider		-0.00556*** [0.001]		-0.00342*** [0.001]
facility delivery	0.00211*** [0.001]	0.00273*** [0.001]	-0.00137* [0.001]	-0.000999 [0.001]
mother had TT injection	-0.00856*** [0.001]	-0.00814*** [0.001]	-0.00619*** [0.001]	-0.00594*** [0.001]
delivery by C-section	0.0101*** [0.001]	0.0103*** [0.001]	0.00106 [0.001]	0.00117 [0.001]
child was breastfed			-0.0501*** [0.002]	-0.0501*** [0.002]
N	689319	689319	522970	522970
Adjusted for confounding	**yes**	**yes**	**yes**	**yes**

All regressions include PSU fixed effects. ***, ** and * denote significance at the 1%, 5%, and 10% levels, respectively. Std. Errors in square brackets and are clustered at PSU level. Control variables include: Mother's age, marital status and educational achievement, whether she heads the HH, child's sex and birth order and spacing, month of birth, whether it was a multiple birth and HH wealth quintile.

Table A4: Associations between nutritional outcomes and mediator variables

	Low Birthweight		Stunting		Underweight	
	(1)	(2)	(1)	(2)	(1)	(2)
at least 1 ANC visit	-0.0349*** [0.004]	-0.0168*** [0.004]	-0.0458*** [0.003]	-0.0388*** [0.003]	-0.0308*** [0.002]	-0.0225*** [0.003]
at least 4 ANC visits & skilled ANC provider		-0.0274*** [0.002]		-0.0159*** [0.002]		-0.0190*** [0.002]
mother had TT injection	-0.00721*** [0.002]	-0.00532*** [0.002]	0.0000754 [0.002]	0.000984 [0.002]	-0.00566*** [0.002]	-0.00458*** [0.002]
child was breastfed			-0.0264*** [0.005]	-0.0264*** [0.005]	-0.0154*** [0.004]	-0.0153*** [0.004]
child ever got vaccine			0.0539*** [0.004]	0.0546*** [0.004]	-0.00196 [0.003]	-0.00107 [0.003]
N	380570	380570	475936	475936	486040	486040
Adjusted for confounding	**yes**	**yes**	**yes**	**yes**	**yes**	**yes**

All regressions include PSU fixed effects. ***, ** and * denote significance at the 1%, 5%, and 10% levels, respectively. Std. Errors in square brackets and are clustered at PSU level. Control variables include: Mother's age, marital status and educational achievement, whether she heads the HH, child's sex and birth order and spacing, month of birth, whether it was a multiple birth and HH wealth quintile.

Table A5: Associations between the exposure variables and full set of control variables

	Neonatal Mortality	Infant Mortality	Low Birthweight	Stunting	Underweight
Maternal education *[reference: no education]*					
Primary or incompl. Secondary	-0.00247*** [0.001]	-0.00539*** [0.001]	-0.0191*** [0.002]	-0.0447*** [0.002]	-0.0356*** [0.002]
Secondary or higher	-0.00566*** [0.001]	-0.00890*** [0.001]	-0.0350*** [0.002]	-0.0785*** [0.003]	-0.0460*** [0.002]
Maternal age at birth *[reference: ≤ 17yrs]*					
17 - 19 years	-0.00474*** [0.001]	-0.00682*** [0.002]	-0.00926** [0.004]	-0.0477*** [0.005]	-0.0340*** [0.004]
20 - 24 years	-0.00735*** [0.001]	-0.0105*** [0.002]	-0.0205*** [0.004]	-0.0714*** [0.004]	-0.0477*** [0.004]
25 - 29 years	-0.00645*** [0.001]	-0.00963*** [0.002]	-0.0218*** [0.004]	-0.0970*** [0.005]	-0.0545*** [0.004]
30 years or older	-0.000352 [0.001]	-0.00881*** [0.002]	-0.00879** [0.004]	-0.114*** [0.005]	-0.0567*** [0.004]
Mother is working	0.00299*** [0.000]	0.000925 [0.001]	-0.000101 [0.001]	0.0155*** [0.002]	0.00591*** [0.001]
Mother is HH Head	-0.000972 [0.001]	-0.0000246 [0.001]	-0.00123 [0.002]	0.00701** [0.003]	-0.00259 [0.002]
Mother is married	-0.00134** [0.001]	-0.00610*** [0.001]	-0.00988*** [0.002]	-0.00849*** [0.002]	-0.0106*** [0.002]
Child is female	-0.00451*** [0.000]	-0.00217*** [0.001]	0.0208*** [0.001]	-0.0399*** [0.001]	-0.0220*** [0.001]
Multiple birth	0.0970*** [0.004]	0.0607*** [0.005]	0.391*** [0.010]	0.155*** [0.009]	0.148*** [0.008]
Birth order *[reference: First born child]*					
Second child	-0.00904*** [0.001]	-0.00495*** [0.001]	-0.0265*** [0.002]	0.0290*** [0.002]	0.00545*** [0.002]
Third child	-0.0108*** [0.001]	-0.00429*** [0.001]	-0.0342*** [0.002]	0.0456*** [0.003]	0.0137*** [0.002]
Fourth child	-0.0118*** [0.001]	-0.00484*** [0.001]	-0.0350*** [0.003]	0.0574*** [0.003]	0.0194*** [0.003]
Fifth or later born child	-0.0115*** [0.001]	-0.00392*** [0.001]	-0.0417*** [0.003]	0.0835*** [0.003]	0.0276*** [0.003]
Birth spacing ≤ 18 months	0.0218*** [0.001]	0.0234*** [0.002]	0.0240*** [0.004]	0.0462*** [0.004]	0.0333*** [0.003]
Wealth quintiles *[reference: poorest 20%]*					
Second quintile	0.00102 [0.001]	-0.00174* [0.001]	-0.00848*** [0.002]	-0.0172*** [0.003]	-0.0120*** [0.002]
Third quintile	0.000917 [0.001]	-0.00246** [0.001]	-0.0121*** [0.003]	-0.0371*** [0.003]	-0.0302*** [0.002]

Fourth quintile	0.000564 [0.001]	-0.00496*** [0.001]	-0.0170*** [0.003]	-0.0602*** [0.003]	-0.0511*** [0.003]
Fifth quintile	0.0000414 [0.001]	-0.00619*** [0.001]	-0.0206*** [0.003]	-0.0977*** [0.003]	-0.0790*** [0.003]
Month of birth	0.0000126 [0.000]	-0.0000336 [0.000]	-0.000283* [0.000]	-0.00372*** [0.000]	-0.00290*** [0.000]
N	**752635**	**574675**	**400426**	**501484**	**512424**
Results are from the main results regressions of table 2 & 3 (model 3) and are adjusted for the full set of control variables and include PSU fixed effects. ***, ** and * denote significance at the 1%, 5%, and 10% levels, respectively. Std. Errors in square brackets and are clustered at PSU level.					

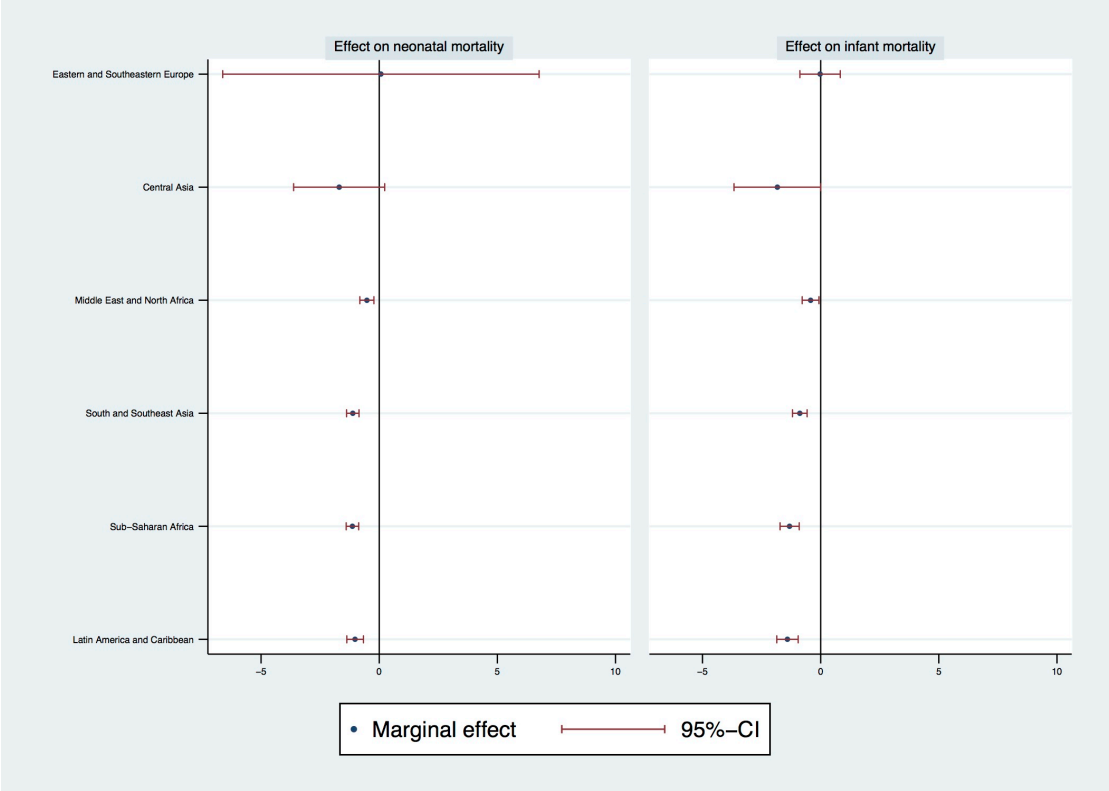
Table A6: Associations between the exposure variables before and after the introduction of the WHO recommendation (Year 2002)

Neonatal Mortality	**Before 2002 (1990-2002)**			**After 2002 (2003-2013)**		
	(1)	**(2)**	**(3)**	**(1)**	**(2)**	**(3)**
at least 1 ANC visit	-0.0130*** [0.001]	-0.0129*** [0.001]	-0.00983*** [0.001]	-0.00798*** [0.001]	-0.00755*** [0.001]	-0.00534*** [0.001]
at least 4 ANC visits & skilled ANC provider			-0.00702*** [0.001]			-0.00453*** [0.001]
N	320338	320338	320338	432297	432297	432297
Infant Mortality	**Before 2002 (1990-2002)**			**After 2002 (2003-2013)**		
at least 1 ANC visit	-0.0152*** [0.001]	-0.0126*** [0.001]	-0.00936*** [0.002]	-0.00987*** [0.001]	-0.00827*** [0.001]	-0.00733*** [0.001]
at least 4 ANC visits & skilled ANC provider			-0.00730*** [0.001]			-0.00189** [0.001]
N	244729	244729	244729	329946	329946	329946
Low Birthweight	**Before 2002 (1990-2002)**			**After 2002 (2003-2013)**		
at least 1 ANC visit	-0.0404*** [0.005]	-0.0352*** [0.005]	-0.0181*** [0.006]	-0.0455*** [0.006]	-0.0416*** [0.006]	-0.0202*** [0.006]
at least 4 ANC visits & skilled ANC provider			-0.0259*** [0.003]			-0.0299*** [0.002]
N	145426	145426	145426	255000	255000	255000
Stunting	**Before 2002 (1990-2002)**			**After 2002 (2003-2013)**		
at least 1 ANC visit	-0.0753*** [0.004]	-0.0416*** [0.004]	-0.0333*** [0.004]	-0.0586*** [0.004]	-0.0383*** [0.004]	-0.0335*** [0.004]
at least 4 ANC visits & skilled ANC provider			-0.0187*** [0.003]			-0.00964*** [0.003]
N	217791	217791	217791	283693	283693	283693
Underweight	**Before 2002 (1990-2002)**			**After 2002 (2003-2013)**		
at least 1 ANC visit	-0.0534*** [0.003]	-0.0299*** [0.003]	-0.0204*** [0.003]	-0.0463*** [0.003]	-0.0338*** [0.003]	-0.0257*** [0.004]
at least 4 ANC visits & skilled ANC provider			-0.0214*** [0.003]			-0.0163*** [0.002]
N	223491	223491	223491	288933	288933	288933

Adjusted for confounding	no	yes	yes	no	yes	yes

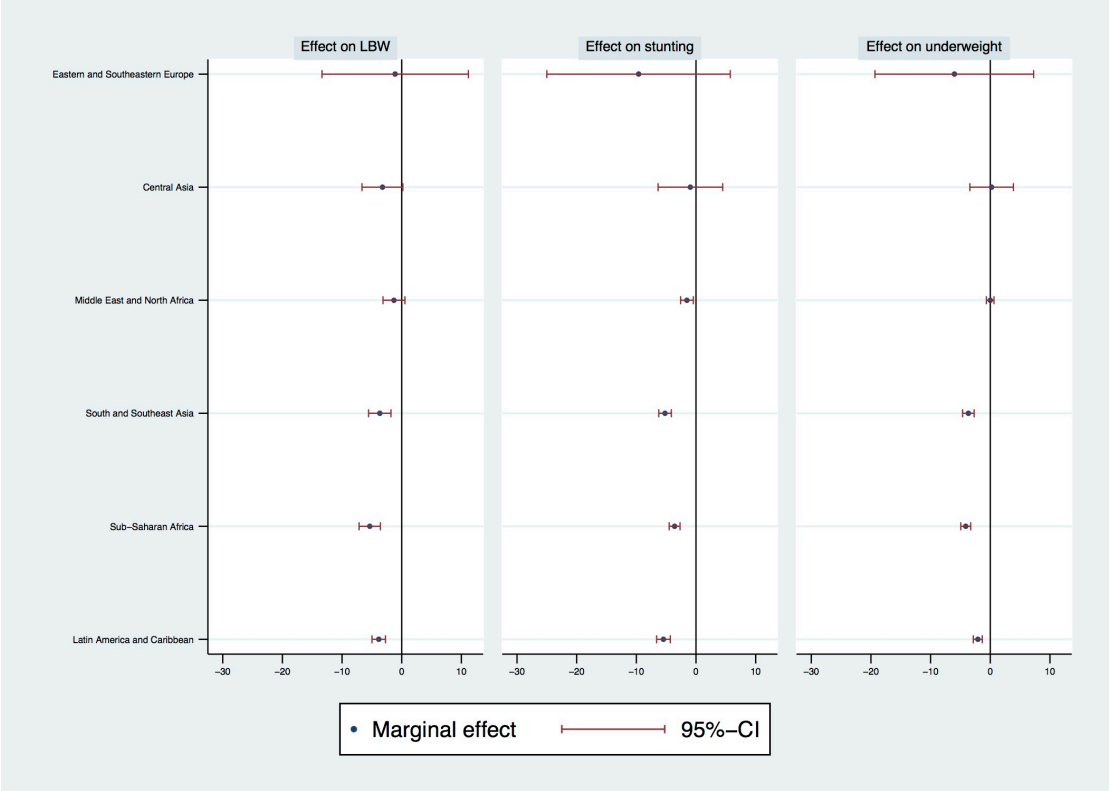
All regressions include PSU fixed effects. ***, ** and * denote significance at the 1%, 5%, and 10% levels, respectively. Std. Errors in square brackets and are clustered at PSU level. Control variables include: Mother's age, marital status and educational achievement, whether she heads the HH, child's sex and birth order and spacing, month of birth, whether it was a multiple birth and HH wealth quintile.

Figure A1: Associations between mortality outcomes and ANC attendance by world region



Figures show marginal effects and 95% confidence intervals for binary indicator that the mother attended at least one ANC visit (region-wise regressions). The estimated model corresponds to the specification (2) from table 2 & 3. All regressions include PSU fixed effects and the full set of covariates.

Figure A2: Associations between nutritional outcomes and ANC attendance by world region



Figures show marginal effects and 95% confidence intervals for binary indicator that the mother attended at least one ANC visit (region-wise regressions). The estimated model corresponds to the specification (2) from table 2 & 3. All regressions include PSU fixed effects and the full set of covariates.

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	2-3
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	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
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	6
		(*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	6-7
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*
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	6,8
		(*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	8
		(*e*) Describe any sensitivity analyses	

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
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9 (table A1)
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
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	*9*
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	9-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-10
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	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	
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.