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Disparities in adverse pregnancy outcomes for short and long birth intervals in Bangladesh: evidence from six Bangladesh Demographic and Health Surveys, 1996-2014

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3 **1 Disparities in adverse pregnancy outcomes for short and long birth intervals in**
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5 **2 Bangladesh: evidence from six Bangladesh Demographic and Health Surveys, 1996-**
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7 **3 2014**
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50
51 23 study, acknowledgement, author's contribution, conflict of interest, tables and figures)

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55 25

26 **ABSTRACT**

27 **Objective**

28 To examine the effect of short (<36 months) and long (≥ 60 months) birth intervals on adverse
29 pregnancy outcomes in Bangladesh.

30 **Design, setting and participants**

31 We analysed data from six Bangladesh Demographic and Health Surveys (1996-1997, 1999-
32 2000, 2004, 2007, 2011 and 2014). We included all singleton non-first live births, most
33 recently born to the mothers within five years preceding each survey (n=21,382). We defined
34 birth interval according to previous literature which suggests that between 36 and 59 months
35 is the most ideal interval. Bivariate and multivariable analyses were conducted to obtain the
36 crude and adjusted odds ratio (aOR) respectively to assess the odds of first-day neonatal
37 death, early neonatal death and small birth size for both short (<36 months) and long (≥ 60
38 months) spacing between births.

39 **Main outcome measures**

40 First-day neonatal death, early neonatal death and small birth size.

41 **Results**

42 In the multivariable analysis, compared to births spaced 36-59 months, infants with birth
43 intervals of less than 36 months were associated with the increased odds of first-day neonatal
44 death (aOR: 2.11, 95% CI: 1.17, 3.78) and early neonatal death (aOR: 1.58, 95% CI: 1.13,
45 2.22). Compared to births spaced 36-59 months, infants with birth interval of ≥ 60 months,
46 were associated with the increased odds of first-day neonatal death (aOR: 2.02, 95% CI: 1.10,
47 3.73) and small birth size (aOR: 1.17, 95% CI: 1.02, 1.34). When there was a history of
48 pregnancy loss, there was an increase in the odds of first-day and early neonatal death for
49 both short and long birth intervals, although there was no association.

50 **Conclusions**

51 Birth intervals shorter than 36 months and longer than 59 months are associated with the
52 increased risk of adverse perinatal outcomes. Care-providers, program managers and
53 policymakers should focus on promoting the optimal birth interval between 36-59 months in
54 postpartum family planning.

55 **Key words:** Pregnancy outcome, birth interval, first-day neonatal death, early neonatal death,
56 small birth size, Bangladesh

58 **Strengths and limitations of this study**

- 59 • The main strength of this study is the use of a large sample from six nationally
60 representative surveys of Bangladesh with a very high response (98%).
- 61 • We used the information of the most recent births within the 5 years preceding the
62 surveys in order to minimise recall bias.
- 63 • Our study is the first in Bangladesh which analysed the effect of birth intervals and
64 other risk factors for first-day neonatal mortality.
- 65 • Demographic and Health Survey data is cross-sectional, which reduces the ability to
66 infer causation.
- 67 • Demographic and Health Survey data uses maternal perceptions of infant birth size as
68 a proxy for birthweight which may be a limitation.

70 BACKGROUND

71 Adverse pregnancy outcomes such as stillbirth, early neonatal mortality and low birthweight
72 are of considerable public health significance. Globally, perinatal mortality (stillbirth and
73 early neonatal mortality) accounts for more than 6 million deaths every year. Of those,
74 approximately 2 million newborns die in the early neonatal period.¹ The risk is greatest on the
75 first day of life, approximately 1 million newborns die within the first 24 hours.¹ Further, low
76 birthweight, occurs in more than 20 million newborns worldwide, which is a major indicator
77 of perinatal mortality and contributes to up to 80% of neonatal mortality.² The greatest
78 proportion of perinatal deaths and low birthweight (97-99%) occur in Low and Middle-
79 Income Countries (LMIC).³

80 Several interventions have been suggested to address adverse pregnancy outcomes, such as
81 pregnancy spacing.⁴ Both short and long birth intervals have been reported to be associated
82 with an increased risk of a number of adverse perinatal outcomes.^{5 6} Current World Health
83 Organization (WHO) guidelines recommend an interval of at least 24 months before
84 attempting the next pregnancy after a live birth (i.e. birth-to-pregnancy interval) in order to
85 reduce any adverse pregnancy outcomes.⁷ Thus, the birth-to-birth interval should be at least
86 33 months by including nine months of pregnancy to the recommended 24 months.⁸ In an
87 analysis of Demographic and Health Survey data from 17 developing countries, Rutstein
88 suggested that the optimal birth interval should be between 36 and 59 months as each birth
89 interval less than 36 and more than 59 months showed a tendency towards neonatal mortality
90 and morbidity.⁹ The WHO highlighted the necessity of future research investigating the
91 association between birth interval and adverse pregnancy outcomes.⁷

92 Bangladesh has high perinatal mortality (44 per 1000 pregnancies) and morbidity,¹⁰ where
93 birth spacing remains a problem.¹¹ Between the year 1993 and 2014, though the median birth

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3 94 interval increased by 49% (from 35 months to 52 months), approximately 30% of non-first
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5 95 births occurred within less than 36 months (7 months to 35 months) following the previous
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7 96 birth.¹⁰ However, another 40% of non-first births occurred following a birth interval of more
8
9 97 than 59 months.¹⁰ Of the papers investigating birth interval in Bangladesh, most have
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11 98 focussed on the effect of short birth interval and have not considered a long birth interval as a
12
13 99 risk of adverse perinatal outcome.^{12 13} Given the changing demographics in Bangladesh and
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16 100 increase in proportion of longer birth intervals, our objective therefore was to examine
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18 101 whether the preceding birth interval (short or long) was independently associated with
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20 102 increased risk of adverse pregnancy outcomes including first-day neonatal mortality, early
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22 103 neonatal mortality and low birthweight using pooled data from the Bangladesh Demographic
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24 104 and Health Surveys.

105 **METHODS**

106 **Data source**

107 We used the Bangladesh Demographic and Health Survey (BDHS) data from the years;
108 1996-1997, 1999-2000, 2004, 2007, 2011 and 2014. BDHS is a nationally representative
109 household survey carried out every three to four years under the authority of the National
110 Institute of Population Research and Training of the Ministry of Health and Family Welfare.
111 The survey employed a two-stage stratified cluster-sampling design with rural and urban
112 samples to collect information from ever-married women aged 15-49 years and ever-married
113 men 15-54 years about demographic and health status. Data were obtained from the website;
114 www.measuredhs.com. The BDHS consists of three types of questionnaires: household,
115 women, and men. Our analysis was limited to the information obtained from the women's
116 and household questionnaires. We pooled the data files into a dataset and analysed the live
117 births occurring during the five years preceding the surveys. In our analysis, we included the

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3 118 data from all singleton, non-first, most recent live-born children within the five years
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5 119 preceding the six BDHSs, 1996-1997, 1999-2000, 2004, 2007, 2011 and 2014.
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8 120 **Outcome variables**

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10 121 We conducted three analyses, with three different outcome variables-‘first-day neonatal
11
12 122 death’, ‘early neonatal death’ and ‘small birth size’. First-day deaths were defined as deaths
13
14 123 during the first 24 hours after birth (day 0) among live-born children and early neonatal
15
16 124 deaths were deaths between the age of 0 to 6 days among live-born children. These two
17
18 125 outcome variables overlap, but conform to standard definitions. Estimates about birthweight
19
20 126 are not collected by the BDHS. ‘Mother’s perception of the baby’s birth size’ is routinely
21
22 127 used as a proxy indicator of birthweight. For our analysis, we defined low birthweight as
23
24 128 infants whose mother’s perception of size was either ‘very small’ or ‘smaller than average’.
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26 129 Each of the outcome variables was considered dichotomous for this analysis as yes (1) or no
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28 130 (0).
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33 131 **Exposure variable**

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35 132 The main exposure variable used in our analysis was the length of the preceding birth interval
36
37 133 as a measure of birth spacing. This was measured as the number of months between two
38
39 134 successive live births.^{9 14} We followed Rutstein’s recommendation regarding optimal birth
40
41 135 interval of 36-59 months for our analysis.⁹ We categorised preceding birth interval in months
42
43 136 as short (<36 months) or long (≥ 60 months) birth intervals for our analysis; where the birth
44
45 137 interval of 36–59 months was the reference category.
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49 138 **Covariates**

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51 139 Covariates included maternal age at childbirth (19 years or below, 20-34 years and 35 years
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53 140 or more), maternal education (no education, primary and secondary or higher), birth order (2-
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55 141 3, ≥ 4), maternal Body Mass Index (BMI) (underweight, average, overweight and obese), area
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3 142 of residence (urban and rural), wealth index (poorest quintile, second quintile, middle quintile
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5 143 and richest quintile), maternal employment status during survey (not working and working),
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7 144 desire for pregnancy (yes and no), ever use of contraception (yes and no), number of
8
9 145 Antenatal Care (ANC) visits (none, 1-3 visits and ≥ 4 visits), ANC by Skilled Birth
10
11 146 Attendants (SBA) (yes and no), history of any previous loss of pregnancy (yes and no), sex of
12
13 147 baby (female and male) and region (Dhaka, Barisal, Chittagong, Khulna, Rajshahi, Rangpur
14
15 148 and Sylhet).

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17
18 149 We constructed the wealth index variable using principle component analysis through
19
20 150 ranking the available wealth variables in the pooled BDHS dataset such as housing materials,
21
22 151 type of toilet facility, source of drinking water, type of cooking fuel, availability of
23
24 152 electricity, ownership of assets (radio, television, fridge etc.), adjusted for urban-rural
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26 153 differences. We constructed the 'ever use of contraception' variable from calendar data of
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28 154 women's dataset for each year, where ever use of contraception was recorded if there was any
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30 155 contraceptive practice at anytime.
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34 156 **Data analysis**

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37 157 The 'first-day neonatal mortality' and 'early neonatal mortality' variables were calculated
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39 158 from the birth history data, where age at death was recorded in days if they were less than 30
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41 159 days old. 'Small birth size' was calculated from the birth history data, based on the
42
43 160 perceptions of mothers about their infant's birth size. Frequencies with weighted percentage
44
45 161 were calculated for the selected variables to describe the characteristics of the women who
46
47 162 had a 'first-day neonatal death', an 'early neonatal death' and a 'small birth size baby'. We
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49 163 conducted bivariate analysis to ascertain the association between each of the independent
50
51 164 variables and each outcome separately, and multivariable analysis was performed to obtain
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53 165 the adjusted odds ratio (aOR). The wald test was used to assess statistical significance with
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55 166 95% confidential intervals (CI). The association was adjusted for potential confounders
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3 167 including maternal age at childbirth, birth order, maternal education, maternal wealth index,
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5 168 maternal employment status, area of residence, maternal BMI, maternal desire of pregnancy,
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7 169 ever use of contraceptive method, number of ANC visits, ANC by SBA, history of previous
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9 170 pregnancy loss, sex of infant and region. We followed the direct life table approach to
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11 171 calculate first-day and early neonatal mortality rates per 1000 live births. All analyses were
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13 172 carried out using STATA version 14.2. The 'svy' command was used to calculate the
14
15 173 weighted values.
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19 174 We obtained permission from Monitoring and Evaluation to Assess and Use Results
20
21 175 Demographic and Health Surveys (MEASURE DHS) to download the data from the DHS
22
23 176 online archive. Ethics approval was not required for our analyses', as the data were
24
25 177 anonymous and publicly available.
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28 178 **Patient involvement**

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31 179 No patients were involved in this study.
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34 180 **Figure 1: Flow diagram showing sample selection for first-day neonatal mortality, early** 35 36 181 **neonatal mortality and small birth size analysis**

37 38 39 182 **RESULTS**

40
41 183 Over the six surveys, and approximately 18 years of data, a total of 42, 718 live births were
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43 184 recorded who were born to the mothers aged 15-49 years within the five years preceding the
44
45 185 surveys with a high response (approximately 98%) (Figure 1). From the year 1996 to 2014,
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47 186 there was a substantial decrease in the rate of overall early neonatal mortality (30.5 vs. 23.3
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49 187 deaths per 1000 live births), but in terms of first-day neonatal mortality, we did not find any
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51 188 consistent decrease, rather the rate has increased from 9.3 deaths in 1996 to 10.6 deaths in
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53 189 2014 per 1000 live births (Figure 2). Rates of all three adverse pregnancy outcomes were
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3 190 highest among the first-born infants followed by the infants whose births were spaced less
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5 191 than 36 months (Figure 3).

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7 192 There were 33, 973 singleton live-born infants, most recently born to the mothers within the
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9 193 five years preceding each survey. Of those, 10,722 (32%) were first-born infants who were
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11 194 ineligible as there was no birth interval, which left 21,382 non-first singleton live-born
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13 195 infants in our final analysis for first-day and early neonatal mortality. For small birth size, our
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15 196 analysis consisted of 11,022 singleton live-born children, for the years 1999-2000, 2011 and
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17 197 2014, as the information regarding small birth size was not available for the surveys in 1996-
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19 198 1997, 2004 and 2007.

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23 199 Of the 21,382 non-first singleton most recently live-born infants of six surveys, there were
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25 200 115 first-day and 274 early neonatal deaths. Of 11,022 non-first singleton most recently live-
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27 201 born infants of three surveys, there were 2002 infants with a birth size smaller than average.

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30 202 **Figure 2: Trends in first-day and early neonatal mortality by year of survey (1996-2014)**

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33 203 **Figure 3: First-day neonatal mortality, early neonatal mortality rates per 1000 live**
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35 204 **births and the proportion of small birth size by preceding birth intervals**

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38 205 **First-day neonatal mortality**

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40 206 Nearly half of the infants who died on the first-day (n=49) were born following a short birth
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42 207 interval, another 44 infants who died on day '0' (36.0%) were born following a long birth
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44 208 interval. Overall, mothers of the infants who died on the day '0' were more frequently aged
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46 209 between 20 and 34 years (67.5%, n=82), did not have any formal education (36.4%, n=40),
47
48 210 had a parity 2-3 (63.3%, n=73), had an average BMI (59.2%, n=67), lived in a rural area
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50 211 (79.2%, n=80) and the infant was male (64.1%, n=74) (Table 1).

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53 212 **Early neonatal mortality**
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3 213 A large proportion of deaths in the early neonatal period was attributable to day '0' deaths
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5 214 (42.8%, n=115). Approximately 45% of infants (n=122) who died within 7 days of birth were
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7 215 born following a short birth interval. Also, a relatively higher proportion (29% vs. 26%) of
8
9 216 early neonatal deaths had a long birth interval compared to the recommended birth interval
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11 217 (36-59 months). The socio-demographic characteristics of the mothers of the infants who
12
13 218 died in the early neonatal period was quite similar to the day '0' findings, and the proportion
14
15 219 of early neonatal mortality was highest among infants born to mothers aged 20-34 years
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17 220 (71.5%, n=200), had a parity 2-3 (60.0%, n=163), did not have any formal education (42.0%,
18
19 221 n=116), lived in a rural area (81.0%, n=193), had an average BMI (58.4%, n=156), did not
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21 222 have any ANC (55.2%, n=146) and the infant was male (58.0%, n=162) (Table 1).
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25 **Small birth size**

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27 224 More than one-third of infants with a small birth size (34.6%, n=698) were born with a short
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29 225 birth interval. A similar proportion of infants with a small birth size (34.2%, n=694) were
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31 226 born with a long birth interval. The highest proportion of infants perceived as small birth size
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33 227 were born to the mothers aged 20-34 years (80.0%, n=1599), had a parity 2-3 (65.8%,
34
35 228 n=1322), had no formal education (38.3%, n=751), had an average BMI (54.4%, n=1069),
36
37 229 lived in rural area (79.9%, n=1445), did not have any ANC (51.4%, n=998) and the infant
38
39 230 was female (55.1%, n=1059) (Table 1).
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43 **Association of birth intervals with first-day neonatal mortality**

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45 232 In the multivariable analysis, both short and long birth intervals were associated with the
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47 233 increased odds of first-day neonatal death. Compared to infants born following a birth
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49 234 interval of 36-59 months, infants with a short birth interval were 2.11 times more likely to die
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51 235 within 24 hours of life (95% CI: 1.17, 3.78). We also found that infants born after a long birth
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53 236 interval, compared to those born following a birth interval of 36-59 months had a 2.02 times
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55 237 higher odds of dying within 24 hours of life (95% CI: 1.10, 3.73). In terms of other
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3 238 determinants, maternal age at childbirth of 19 years or less (aOR: 2.51, 95% CI: 1.35, 4.66),
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5 239 maternal non-use of contraception (aOR: 2.20, 95% CI: 1.32, 3.68) and male infants (aOR:
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7 240 1.70, 95% CI: 1.09, 2.64) were associated with the increased odds of first-day neonatal death
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9 241 (Table 2).

242 **Association of birth intervals with early neonatal mortality**

243 After adjustment for potential confounders, early neonatal mortality was associated with a
244 short birth interval, while for long birth intervals there was no association. Compared to the
245 infants with a birth interval of 36-59 months, infants born with a short birth interval had 1.58
246 times higher odds of dying within 7 days of life (95% CI: 1.13, 2.22). Though the odds of
247 early neonatal mortality after a long birth interval compared to the reference group were
248 greater, there was no association (aOR: 1.23, 95% CI: 0.84, 1.81). Other determinants of
249 early neonatal mortality included maternal age 19 years or less (aOR 1.53, 95% CI: 1.02,
250 2.28), maternal non-use of contraception (aOR: 1.89, 95% CI: 1.35, 2.64) and being a male
251 infant (aOR: 1.32, 95% CI: 1.01, 1.73) (Table 2).

252 **Association of birth intervals with small birth size**

253 Long birth intervals appeared to be associated with the increased odds of small birth size
254 compared to the reference birth interval (aOR: 1.17, 95% CI: 1.02, 1.34), while for short birth
255 intervals, the odds of small birth size were smaller (aOR: 1.04, 95% CI: 0.89, 1.20) compared
256 to the reference birth interval. Other factors associated with small birth size were mothers
257 being classified as poorest (aOR: 1.30, 95% CI: 1.05, 1.61), second poorest (aOR: 1.34, 95%
258 CI: 1.09, 1.64) on wealth index, mothers being underweight by BMI (aOR: 1.19, 95% CI:
259 1.05, 1.34) and maternal non-use of contraception (aOR: 1.23, 95% CI: 1.06, 1.42). Unlike
260 first-day and early neonatal mortality, male infants were less likely to be born small (aOR:
261 0.71, 95% CI: 0.63, 0.80) compared to female infants (Table 2).

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3 262 A history of pregnancy loss can be a determinant of birth interval and we therefore restricted
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5 263 our analysis to the children whose mothers had a history of pregnancy loss for all three
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7 264 outcomes. However, we found no relationship for either short or long birth intervals with all
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9 265 three outcomes, though for both short and long birth intervals there was an increase in the
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11 266 odds for first-day and early neonatal death (Table 3).

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3 268 **DISCUSSION**

4
5 269 This is a large cross-sectional study of a large sample size over an 18-year time period. There
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7 270 was a marked decline in the overall rate of early neonatal mortality between the year 1996
8
9 271 and 2014, whereas the rate of first-day neonatal death slightly increased. A major proportion
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11 272 of infants who died on the first-day, or in the first week or with a small birth size were born
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13 273 before the recommended optimal period of birth interval (36–59 months). We found that a
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15 274 birth-to-birth interval shorter than 36 months was associated with an increased odds of
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17 275 multiple adverse pregnancy outcomes including first-day neonatal mortality and early
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19 276 neonatal mortality. Also, birth-to-birth interval longer than 59 months was associated with an
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21 277 increased odds of first-day neonatal mortality and small birth size.
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25 278 Several studies have reported the association of a short birth interval with perinatal or
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27 279 neonatal mortality.^{15 16} However, to the best of our knowledge, no prior research has
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29 280 examined the effect of birth interval on first-day neonatal mortality individually. We found
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31 281 that a short birth-to-birth interval of less than 36 months was associated with higher odds of
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33 282 first-day neonatal mortality. Further, we found that the odds of early neonatal mortality were
34
35 283 also greater among infants who were born following a short birth interval. This is consistent
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37 284 with the findings of a few earlier investigations from LMIC's which examined the effect of
38
39 285 short birth intervals on perinatal, early neonatal or neonatal mortality.^{15 16} Similar to our
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41 286 findings, a previous study conducted in India reported an association of neonatal death with a
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43 287 birth interval of less than 36 months (aOR: 1.78, 95% CI: 1.63, 1.94), compared to births
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45 288 spaced 36–59 months.¹⁶ Again, an analysis of 47 Demographic Health Surveys from LMIC
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47 289 also supports our finding of higher odds of early neonatal mortality for short birth intervals,
48
49 290 though this analysis has used a slightly different definitions of both short (<24 months) and
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51 291 the reference category birth interval (24-<60 months).¹⁷ Also, our finding is in line with the
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53 292 finding of a previous study conducted in Matlab, Bangladesh, where they reported an
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3 293 increased risk of very short birth intervals (less than 15 months) on early neonatal mortality
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5 294 compared to those born after 36-59 months, though in their study the risk of early neonatal
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7 295 mortality goes down as the birth interval increases up to a minimum of 24-59 months, which
8
9 296 is not consistent with our findings.¹² Furthermore, we did not find any significant association
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11 297 between short birth interval and small birth size, although infants born following a short
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13 298 interval were at increased odds of being born with a small birth size. In the BDHS,
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15 299 birthweight is not routinely collected and birth size is based on maternal perception which
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17 300 could lead to some errors in the estimation of small birth size and may be responsible for this
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19 301 non-association. However, the direction of the effect is consistent with several earlier
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21 302 investigations including a meta-analysis of 69 studies from both developing and developed
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23 303 countries.^{4 15 18} Several hypotheses have been proposed to explain the association of short
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25 304 birth interval on adverse pregnancy outcomes.¹⁹ One of the most frequently used hypotheses
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27 305 is the maternal nutritional depletion phenomenon, which has been defined by Winkvist et al.
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29 306 as a negative change in maternal nutritional status during a reproductive cycle, mostly due to
30
31 307 the biological competition between mother and the growing fetus.²⁰⁻²² Short birth spacing
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33 308 does not allow mothers sufficient time to restore nutritional reserves needed to support fetal
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35 309 growth and development during the subsequent pregnancy. This eventually causes maternal
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37 310 nutritional depletion that leads to the increase risk of adverse pregnancy outcomes among the
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39 311 births spaced after a short interval. Another explanation is that the association of short birth
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41 312 intervals and adverse pregnancy outcomes could be confounded by other factors including
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43 313 young maternal age, lower socio-economic status and lower utilisation of health services.^{23 24}
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45 314 In our analysis, after adjusting for maternal age, socio-economic factors, and maternal
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47 315 characteristics as well as health service related factors, short birth interval remained
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49 316 associated with first-day and early neonatal mortality which is in line with other studies from
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51 317 both LMIC and high income countries which controlled for similar variables.^{12 14 25 26}
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3 318 Our study further identified the association of long birth interval with adverse perinatal
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5 319 outcomes and found that infants born after a long birth interval were associated with greater
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7 320 odds of first-day neonatal mortality. The effect of long birth interval for early neonatal
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9 321 mortality was also greater but was not significant. There are only a few published studies on
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11 322 the effect of a long birth interval on adverse pregnancy outcome in LMIC and the results are
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13 323 conflicting.^{4 15 16} In contrast to our findings, a previous investigation conducted in India,
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15 324 which examined the effect for long birth intervals for perinatal death, did not find any
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17 325 association,¹⁵ and a pooled analysis of 47 Demographic Health Surveys examined the effect
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19 326 of longer interval for neonatal mortality and found that the odds were lower for the longer
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21 327 preceding birth intervals (≥ 60 months) (OR: 0.80, 95% CI: 0.67, 0.95) compared to the birth
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23 328 interval of 24-<60 months.¹⁷ The inconsistency in findings could be attributed to
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25 329 methodological differences in both the reference category (36-59 months vs. 24-<60 months)
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27 330 of the main exposure variable and the difference in the outcome variable (early neonatal
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29 331 mortality vs. neonatal mortality). However, our findings are consistent with a meta-analysis
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31 332 which reported higher odds of early neonatal mortality with a longer interval,⁴ and Rutstein's
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33 333 study which analysed data from 17 developing countries with the same finding.⁹ Again, we
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35 334 found that a long birth interval was associated with a greater odds of small birth size. This is
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37 335 similar to a few prior studies which also reported the detrimental effect of a long birth
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39 336 interval on birth size.^{4 15 27} The increased odds of adverse pregnancy outcomes for long birth
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41 337 intervals may be due to some concurrent factors such as advanced maternal age and previous
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43 338 history of pregnancy loss. In an earlier investigation, Zhu et al. explained the association
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45 339 between long birth intervals and adverse pregnancy outcomes through the gradual decline in
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47 340 the maternal physiological and anatomical capacities of the reproductive system,
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49 341 hypothesising that if a woman does not conceive for an extended time after a delivery, her
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51 342 physiological characteristics may return to her primigravid state.²⁸
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3 343 We also examined disparities in first-day neonatal mortality, early neonatal mortality and
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5 344 small birth size by several other important factors. Consistent with several previous studies
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7 345 from LMIC's including Bangladesh, we found that young maternal age, maternal non-use of
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9 346 contraception and male sex of infant were associated with greater odds of first-day and early
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11 347 neonatal mortality.^{29 30} Regarding small birth size, the two poorest quintiles, maternal
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13 348 underweight, maternal non-use of contraception and female sex of infant were determinants
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15 349 of small birth size, similar to previous investigations.^{31 32}

18 350 **Strengths and limitations**

20 351 The main strength of our study is that it was based on a large nationally representative sample
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22 352 from six surveys within an 18-year time period in a single country which would improve the
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24 353 homogeneity of the data. We restricted our analysis to the most recent live births within the
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26 354 five years prior to the interview date to minimise recall bias. Furthermore, we were able to
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28 355 add a number of potential confounding factors. We acknowledge some methodological
29
30 356 limitations. First, this is a cross-sectional data, which may limit the identification of a causal
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32 357 relationship between the birth interval and adverse pregnancy outcomes. Secondly, BDHS
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34 358 data relies on maternal recall and report of the information regarding preceding birth intervals
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36 359 and the days of infant deaths, which is subject to recall bias. There is a possibility of
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38 360 underreporting of infant deaths, as birth histories and infant survival information were only
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40 361 collected from surviving mothers and there is a strong association between maternal and
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42 362 infant deaths. Also, in our analysis, we were unable to include the variable regarding the
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44 363 history of immediate previous adverse outcome such as stillbirth, miscarriage etc. which is a
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46 364 major determinant of adverse perinatal outcomes in the subsequent pregnancy. Also, previous
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48 365 adverse pregnancy outcome has an influence on birth interval; as mothers who had a previous
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50 366 pregnancy loss may rush into a pregnancy without properly recovering from the pregnancy
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52 367 loss. A previous investigation conducted in Bangladesh, reported that a short birth interval
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3 368 increases the risk of neonatal death of the subsequent infant after a previous adverse neonatal
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5 369 death.³³ We were able to include the variable ‘ever had a pregnancy loss’ in our analysis, but
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7 370 none of our outcome variables was significant, though stratifying by that variable increased
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9 371 the effect sizes of first-day and early neonatal mortality for both short and long birth
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11 372 intervals.

14 373 **CONCLUSIONS**

16 374 Our analysis supports the reduced risk of adverse pregnancy outcomes following a birth-to-
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18 375 birth interval of 36-59 months which is consistent with the WHO recommendation of a birth-
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20 376 to-pregnancy interval of 24 months. Our results highlight several important implications for
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22 377 care-providers, program managers and policymakers by suggesting that a preceding birth
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24 378 interval of 36-59 months could prevent adverse pregnancy outcomes including first-day
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26 379 neonatal death, early neonatal death and low birthweight. Promoting an optimal birth interval
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28 380 of 36-59 months in postpartum family planning is needed.

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42
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47 387 **Authors’ contributions**

49 388 MKN, CRG and AA conceptualised and designed the study. MKN performed the literature
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51 389 review. MKN, CRG, MTI and TH performed statistical analysis. MKN and CRG drafted the
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53 390 manuscript. MKN and CRG contributed to the interpretation of the data. CRG, AA and MTI

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3 391 contributed to the critical revision of the manuscript. All the authors read and approved the
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5 392 final manuscript.

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9 394 **Conflict of interest**

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11 395 We declare that we have no conflict of interest.

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Table 1: First-day neonatal mortality, early neonatal mortality and small birth size infants by maternal characteristics in Bangladesh: BDHS 1996-2014

Predictors	First-day neonatal mortality (N= 21,382) n (%) n=115	Early neonatal mortality (N= 21,382) n (%) n=274	Small birth size (N= 11,022) n (%) n=2,002
Preceding birth interval in months			
<36 months	49 (45.2)	122 (45.2)	698 (34.6)
36-59 months	22 (18.8)	70 (26.2)	610 (31.2)
≥ 60 months	44 (36.0)	82 (28.6)	694 (34.2)
Mother's age at childbirth			
≤19 years	20 (21.1)	40 (16.2)	218 (10.7)
20-34 years	82 (67.5)	200 (71.5)	1599 (80.0)
≥35 years	13 (11.4)	34 (12.3)	185 (9.3)
Birth order			
2-3	73 (63.3)	163 (60.0)	1322 (65.8)
≥4	42 (36.7)	111 (40.0)	680 (34.2)
Maternal education			
None	40 (36.4)	116 (42.0)	751 (38.3)
Primary	41 (33.7)	84 (30.6)	618 (29.0)
Secondary or higher	34 (29.9)	74 (27.4)	633 (32.7)
Wealth index			
Poorest quintile	24 (19.6)	71 (23.5)	428 (19.6)
Second quintile	24 (21.6)	63 (24.0)	394 (19.8)
Middle quintile	24 (19.5)	57 (22.2)	389 (19.4)
Fourth quintile	20 (20.2)	35 (13.5)	388 (20.7)
Richest quintile	23 (19.1)	48 (16.8)	403 (20.5)
Employment status			
Currently working	34 (32.1)	70 (28.0)	339 (18.0)
Not working	81 (67.9)	204 (72.0)	1663 (82.0)
Area of residence			
Urban	35 (20.8)	81 (19.0)	557 (20.1)
Rural	80 (79.2)	193 (81.0)	1445 (79.9)
Maternal BMI			
Underweight	27 (23.1)	83 (29.3)	711 (35.3)
Average	67 (59.2)	156 (58.4)	1069 (54.5)
Overweight	16 (13.1)	26 (9.3)	169 (7.9)
Obese	5 (4.6)	9 (3.0)	53 (2.3)
Maternal desire of			

pregnancy			
Yes	77 (63.3)	171 (63.5)	1205 (60.1)
No	38 (36.7)	103 (36.5)	797 (39.9)
Ever use of contraception			
Yes	81 (72.9)	196 (71.9)	1605 (81.1)
No	34 (27.1)	78 (28.1)	397 (18.9)
No. of ANC visits			
None	48 (43.1)	146 (55.2)	998 (51.4)
1-3 visits	46 (40.7)	90 (32.0)	683 (33.7)
≥4 visits	21 (16.2)	38 (12.8)	321 (14.9)
ANC by SBA			
Yes	56 (47.3)	111 (38.6)	817 (38.8)
No	59 (52.7)	163 (61.4)	1185 (61.2)
History of any previous pregnancy loss			
Yes	35 (26.3)	79 (26.2)	435 (21.4)
No	80 (73.7)	195 (73.8)	1567 (78.6)
Sex of infant			
Male	74 (64.1)	162 (58.0)	943 (44.9)
Female	41 (35.9)	112 (42.0)	1059 (55.1)
Region			
Barisal	10 (4.2)	28 (5.5)	176 (4.7)
Chittagong	12 (10.1)	40 (13.9)	463 (25.4)
Khulna	10 (8.2)	27 (9.0)	232 (8.6)
Rajshahi	27 (25.1)	50 (20.9)	227 (13.2)
Rangpur	15 (8.0)	47 (10.7)	235 (8.2)
Sylhet	10 (3.5)	18 (3.5)	281 (7.1)
Dhaka	31 (40.9)	64 (36.5)	388 (32.8)
Year of survey			
1996	16 (14.0)	45 (15.8)	-
1999	13 (10.7)	45 (15.8)	705 (34.2)
2004	22 (20.1)	55 (21.2)	-
2007	19 (17.9)	37 (13.6)	-
2011	29 (24.1)	59 (21.5)	813 (40.1)
2014	16 (13.2)	33 (12.1)	484 (25.7)

Table 2: Adjusted odds ratios for the association between preceding birth intervals and adverse pregnancy outcomes in Bangladesh: BDHS 1996-2014

Predictors	First-day neonatal mortality N=21,382		Early neonatal mortality N=21,382		Small birth size N=11,022	
	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Preceding birth interval in months						
<36 months	2.11 (1.17, 3.78)	<0.05	1.58 (1.13, 2.22)	<0.05	1.04 (0.90, 1.20)	0.08
36-59 months	Reference		Reference		Reference	
≥60 months	2.02 (1.10, 3.73)		1.23 (0.84, 1.81)		1.17 (1.02, 1.34)	
Mother's age at childbirth						
≤19 years	2.51 (1.35, 4.66)	<0.05	1.53 (1.02, 2.28)	<0.05	1.01 (0.83, 1.21)	0.68
20-34 years	Reference		Reference		Reference	
≥35 years	1.34 (0.67, 2.69)		1.46 (0.93, 2.29)		1.10 (0.89, 1.36)	
Birth order						
2-3	Reference		Reference		Reference	
≥4	1.48 (0.88, 2.50)	0.14	1.27 (0.92, 1.75)	0.15	1.02 (0.89, 1.16)	0.81
Maternal education						
None	0.97 (0.49, 1.94)	0.80	0.94 (0.60, 1.46)	0.94	1.09 (0.91, 1.30)	0.05
Primary	1.15 (0.62, 2.11)		0.98 (0.65, 1.50)		0.91 (0.77, 1.07)	
Secondary or higher	Reference		Reference		Reference	
Wealth status						
Poorest quintile	0.76 (0.34, 1.68)	0.89	0.86 (0.53, 1.40)	0.68	1.30 (1.05, 1.61)	<0.05
Second quintile	0.92 (0.43, 1.95)		0.99 (0.61, 1.63)		1.34 (1.09, 1.64)	
Middle quintile	0.97 (0.48, 1.96)		1.09 (0.70, 1.72)		1.12 (0.91, 1.37)	
Fourth quintile	1.15 (0.58, 2.28)		0.80 (0.48, 1.32)		1.12 (0.93, 1.37)	

Richest quintile	Reference		Reference		Reference	
Employment status						
Working	1.59 (0.99, 2.56)	0.05	1.30 (0.96, 1.75)	0.09	1.02 (0.87, 1.19)	0.83
Not working	Reference		Reference		Reference	
Area of residence						
Urban	1.10 (0.64, 1.88)	0.72	1.14 (0.80, 1.63)	0.46	1.09 (0.93, 1.27)	0.28
Rural	Reference		Reference		Reference	
Maternal BMI						
Underweight	0.58 (0.35, 0.97)	<0.05	0.70 (0.52, 0.94)	0.05	1.19 (1.05, 1.34)	<0.05
Average	Reference		Reference		Reference	
Overweight	1.81 (0.90, 3.65)		1.36 (0.80, 2.32)		0.86 (0.70, 1.07)	
Obese	1.84 (0.59, 5.67)		1.23 (0.53, 2.89)		0.86 (0.60, 1.23)	
Maternal desire of pregnancy						
Yes	1.09 (0.71, 1.68)	0.68	1.13 (0.84, 1.51)	0.43	0.92 (0.81, 1.05)	0.22
No	Reference		Reference		Reference	
Ever use of contraception						
Yes	Reference		Reference		Reference	
No	2.20 (1.32, 3.68)	<0.05	1.89 (1.35, 2.64)	<0.001	1.23 (1.06, 1.42)	<0.05
No of ANC visits						
None	0.89 (0.29, 2.73)	0.62	1.61 (0.74, 3.48)	0.48	1.09 (0.84, 1.42)	0.79
1-3 visits	1.21 (0.61, 2.37)		1.16 (0.71, 1.89)		1.03 (0.86, 1.23)	
≥4 visits	Reference		Reference		Reference	
ANC by SBA						
Yes	Reference		Reference		Reference	

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No	1.01 (0.46, 2.19)	0.99	0.78 (0.43, 1.42)	0.42	1.05 (0.83, 1.32)	0.70
History of any previous pregnancy loss						
Yes	1.31 (0.85, 2.03)	0.22	1.27 (0.94, 1.71)	0.12	1.04 (0.91, 1.20)	0.53
No	Reference		Reference		Reference	
Sex of infant						
Male	1.70 (1.09, 2.64)	<0.05	1.32 (1.01, 1.73)	<0.05	0.71 (0.63, 0.80)	<0.001
Female	Reference		Reference		Reference	
Region						
Barisal	0.59 (0.27, 1.30)	<0.05	0.82 (0.51, 1.30)	<0.05	0.74 (0.59, 0.92)	<0.001
Chittagong	0.34 (0.16, 0.71)		0.50 (0.32, 0.77)		1.16 (0.97, 1.38)	
Khulna	0.72 (0.35, 1.50)		0.91 (0.57, 1.44)		0.96 (0.79, 1.17)	
Rajshahi	1.12 (0.63, 1.99)		1.02 (0.68, 1.53)		0.73 (0.60, 0.89)	
Rangpur	0.68 (0.35, 1.29)		0.99 (0.66, 1.51)		0.81 (0.65, 0.99)	
Sylhet	0.83 (0.36, 1.88)		0.92 (0.53, 1.61)		1.24 (1.03, 1.50)	
Dhaka	Reference		Reference		Reference	

*Odds ratios were adjusted for maternal age at childbirth, birth order, maternal education, maternal wealth index, maternal employment status, area of residence, maternal BMI, maternal desire of pregnancy, ever use of contraceptive method, number of ANC visits, ANC by SBA, history of any previous pregnancy loss, sex of infant and region

Table 3: Adjusted odds ratios for the association between preceding birth intervals and adverse pregnancy outcomes by history of pregnancy loss: BDHS 1996-2014

Predictors	First-day neonatal mortality N=21,382		Early neonatal mortality N=21,382		Small birth size N=11,022	
	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Preceding birth interval in months*history of pregnancy loss						
<36 months	2.12 (0.74, 6.13)	0.28	1.77 (0.90, 3.49)	0.19	0.96 (0.69, 1.33)	0.38
36-59 months	Reference		Reference		Reference	
≥60 months	2.15 (0.73, 6.31)		1.74 (0.84, 3.62)		1.18 (0.87, 1.59)	

*Odds ratios were adjusted for maternal age at childbirth, birth order, maternal education, maternal wealth index, maternal employment status, area of residence, maternal BMI, maternal desire of pregnancy, ever use of contraceptive method, number of ANC visits, ANC by SBA, sex of infant and region

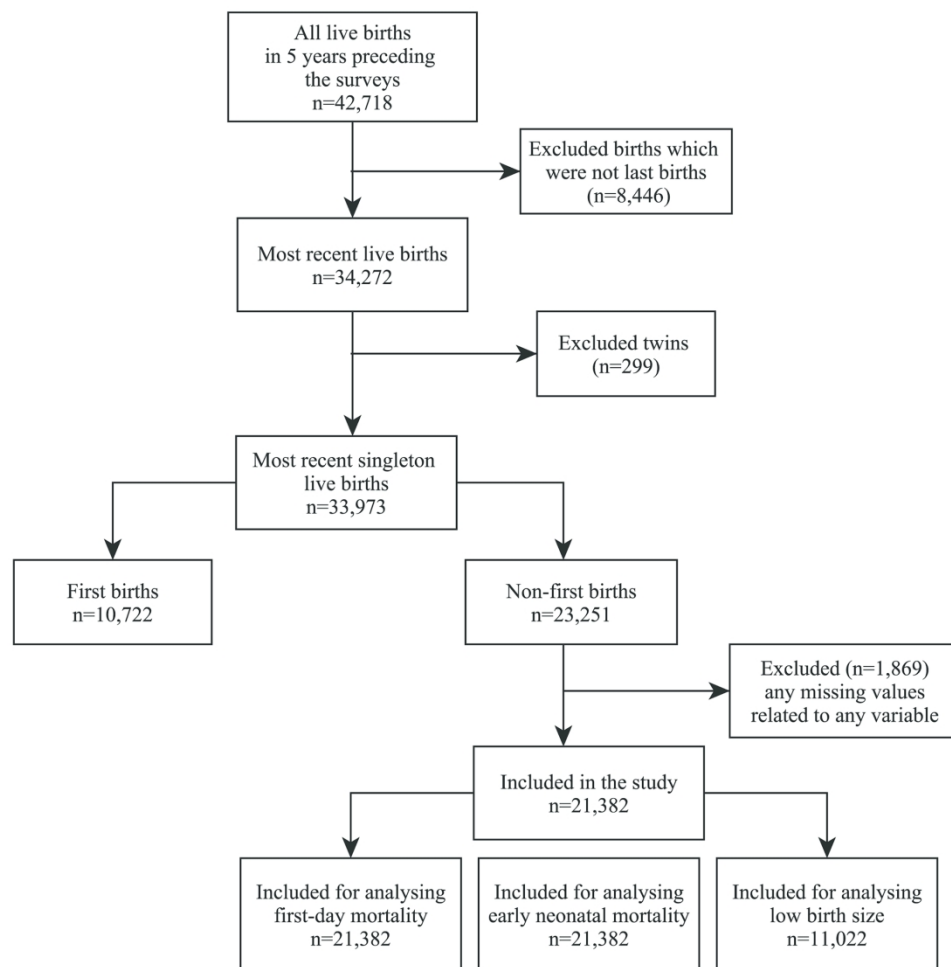


Figure 1: Flow diagram showing sample selection for first-day neonatal mortality, early neonatal mortality and small birth size analysis

203x205mm (300 x 300 DPI)

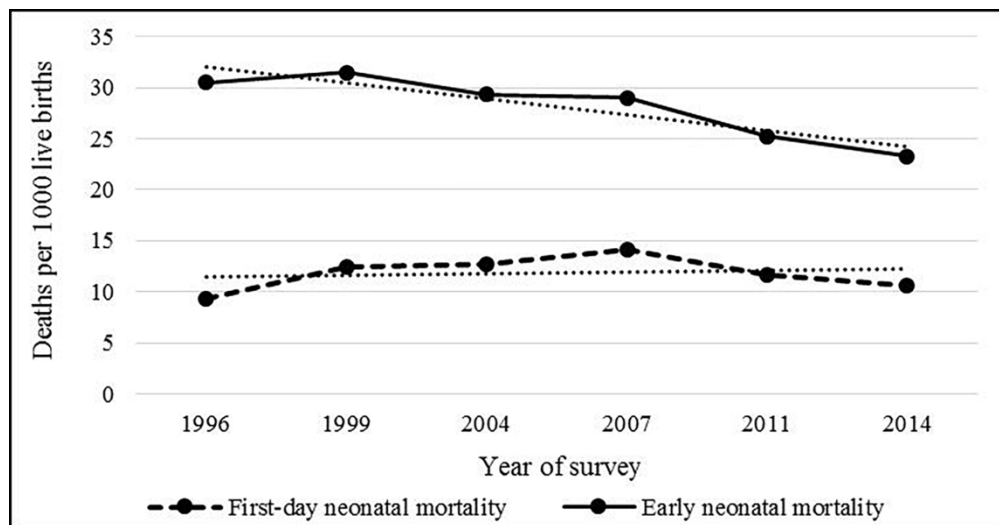


Figure 2: Trends in first-day and early neonatal mortality by year of survey (1996-2014)

191x99mm (300 x 300 DPI)

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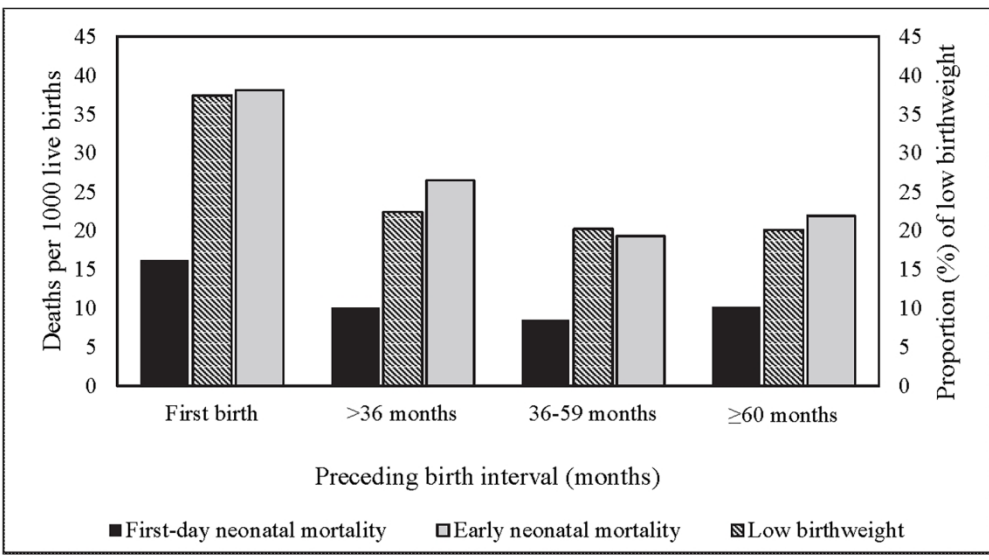


Figure 3: First-day neonatal mortality, early neonatal mortality rates per 1000 live births and the proportion of small birth size by preceding birth intervals

178x99mm (300 x 300 DPI)

BMJ Open

Risk of adverse pregnancy outcomes associated with short and long birth intervals in Bangladesh: evidence from six Bangladesh Demographic and Health Surveys, 1996-2014

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3 **1 Risk of adverse pregnancy outcomes associated with short and long birth intervals in**
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5 **2 Bangladesh: evidence from six Bangladesh Demographic and Health Surveys, 1996-**
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7 **3 2014**
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51
52 23 study, acknowledgement, author's contribution, conflict of interest, tables and figures)

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56 25

26 **ABSTRACT**

27 **Objective**

28 To examine the effect of short (<36 months) and long (≥ 60 months) birth intervals on adverse
29 pregnancy outcomes in Bangladesh.

30 **Design, setting and participants**

31 We analysed data from six Bangladesh Demographic and Health Surveys (1996-1997, 1999-
32 2000, 2004, 2007, 2011 and 2014). We included all singleton non-first live births, most
33 recently born to the mothers within five years preceding each survey (n=21,382). We defined
34 birth interval according to previous literature which suggests that a birth interval between 36
35 and 59 months is the most ideal interval. Bivariate and multivariable analyses were conducted
36 to obtain the crude and adjusted odds ratio (aOR) respectively to assess the odds of first-day
37 neonatal death, early neonatal death and small birth size for both short (<36 months) and long
38 (≥ 60 months) spacing between births.

39 **Main outcome measures**

40 First-day neonatal death, early neonatal death and small birth size.

41 **Results**

42 In the multivariable analysis, compared to births spaced 36-59 months, infants with birth
43 intervals of less than 36 months were associated with the increased odds of first-day neonatal
44 death (aOR: 2.11, 95% CI: 1.17, 3.78) and early neonatal death (aOR: 1.58, 95% CI: 1.13,
45 2.22). Compared to births spaced 36-59 months, infants with birth interval of ≥ 60 months,
46 were associated with the increased odds of first-day neonatal death (aOR: 2.02, 95% CI: 1.10,
47 3.73) and small birth size (aOR: 1.17, 95% CI: 1.02, 1.34). When there was a history of any
48 previous pregnancy loss, there was an increase in the odds of first-day and early neonatal
49 death for both short and long birth intervals, although there was no association.

50 **Conclusions**

51 Birth intervals shorter than 36 months and longer than 59 months are associated with the
52 increased risk of adverse pregnancy outcomes. Care-providers, program managers and
53 policymakers should focus on promoting the optimal birth interval between 36-59 months in
54 postpartum family planning.

55 **Key words:** Pregnancy outcome, birth interval, first-day neonatal death, early neonatal death,
56 small birth size, Bangladesh

58 **Strengths and limitations of this study**

- 59 • The main strength of this study is the use of a large sample from six nationally
60 representative surveys of Bangladesh with a very high response (98%).
- 61 • We used the information of the most recent births within the 5 years preceding the
62 surveys in order to minimise recall bias.
- 63 • Our study is the first in Bangladesh which analysed the effect of birth intervals and
64 other risk factors for first-day neonatal mortality.
- 65 • Demographic and Health Survey data is cross-sectional, which reduces the ability to
66 infer causation.
- 67 • Demographic and Health Survey data uses maternal perceptions of infant birth size as
68 a proxy for birthweight which may be a limitation.

70 BACKGROUND

71 Adverse pregnancy outcomes such as stillbirth, early neonatal mortality and low birthweight
72 are of considerable public health significance. Globally, perinatal mortality (stillbirth and
73 early neonatal mortality) accounts for more than 6 million deaths every year. Of those,
74 approximately 2 million newborns die in the early neonatal period.¹ The risk is greatest on the
75 first day of life, approximately 1 million newborns die within the first 24 hours.¹ Further, low
76 birthweight, occurs in more than 20 million newborns worldwide, which is a major indicator
77 of perinatal mortality and contributes to up to 80% of neonatal mortality.² The greatest
78 proportion of perinatal deaths and low birthweight (97-99%) occur in Low and Middle-
79 Income Countries (LMIC).³

80 Several interventions have been suggested to address adverse pregnancy outcomes, such as
81 pregnancy spacing.⁴ Both short and long birth intervals have been reported to be associated
82 with an increased risk of a number of adverse perinatal outcomes.^{5 6} Current World Health
83 Organization (WHO) guidelines recommend an interval of at least 24 months before
84 attempting the next pregnancy after a live birth (i.e. birth-to-pregnancy interval) in order to
85 reduce any adverse pregnancy outcomes.⁷ Thus, the birth-to-birth interval should be at least
86 33 months by including nine months of pregnancy to the recommended 24 months.⁸ In an
87 analysis of Demographic and Health Survey data from 17 developing countries, Rutstein
88 suggested that the optimal birth interval should be between 36 and 59 months as each birth
89 interval less than 36 and more than 59 months showed a tendency towards neonatal mortality
90 and morbidity.⁹ The WHO highlighted the necessity of future research investigating the
91 association between birth interval and adverse pregnancy outcomes.⁷

92 Bangladesh has high perinatal mortality (44 per 1000 pregnancies) and morbidity,¹⁰ where
93 birth spacing remains a problem.¹¹ Between the year 1993 and 2014, though the median birth

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3 94 interval increased by 49% (from 35 months to 52 months), approximately 30% of non-first
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5 95 births occurred within less than 36 months (7 months to 35 months) following the previous
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7 96 birth.¹⁰ However, another 40% of non-first births occurred following a birth interval of more
8
9 97 than 59 months.¹⁰ Of the papers investigating birth interval in Bangladesh, most have
10
11 98 focussed on the effect of short birth interval and have not considered a long birth interval as a
12
13 99 risk of adverse perinatal outcome.^{12 13} Given the changing demographics in Bangladesh and
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16 100 increase in proportion of longer birth intervals, our objective therefore was to examine
17
18 101 whether the preceding birth interval (short or long) was independently associated with
19
20 102 increased risk of adverse pregnancy outcomes including first-day neonatal mortality, early
21
22 103 neonatal mortality and low birthweight using pooled data from the Bangladesh Demographic
23
24 104 and Health Surveys (BDHS).

105 **METHODS**

106 **Data source**

107 We used the BDHS data from the years; 1996-1997, 1999-2000, 2004, 2007, 2011 and 2014.
108 BDHS is a nationally representative household survey carried out every three to four years
109 under the authority of the National Institute of Population Research and Training of the
110 Ministry of Health and Family Welfare. The survey employed a two-stage stratified cluster-
111 sampling design with rural and urban samples to collect information from ever-married
112 women aged 15-49 years and ever-married men 15-54 years about demographic and health
113 status. Data were obtained from the website; www.measuredhs.com. The BDHS consists of
114 three types of questionnaires: household, women, and men. Our analysis was limited to the
115 information obtained from the women's and household questionnaires. We pooled the data
116 files from six surveys into a dataset and analysed the live births occurring during the five
117 years preceding the surveys. Demographic and Health Survey program employs standardised
118 data collection procedures using standard model questionnaires to ensure consistent content

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3 119 over time and across countries allowing comparability across populations cross-sectionally
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5 120 and over time.¹⁴ We selected six surveys in this pooled analysis based on the similarities in
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7 121 sampling design, comparability of survey questionnaires for focus variables of this analysis,
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9 122 and availability of data for the pooled analysis. In our analysis, we included the data from all
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11 123 singleton, non-first, most recent live-born children within the five years preceding the six
12
13 124 BDHSs, 1996-1997, 1999-2000, 2004, 2007, 2011 and 2014.

125 **Outcome variables**

126 We conducted three analyses', with three different outcome variables- 'first-day neonatal
127 death', 'early neonatal death' and 'small birth size'. First-day deaths were defined as deaths
128 during the first 24 hours after birth (day 0) among live-born children and early neonatal
129 deaths were deaths between the age of 0 to 6 days among live-born children. These two
130 outcome variables overlap, but conform to standard definitions. We used 'small birth size' as
131 a proxy for low birthweight. Estimates about birthweight are not collected by the BDHS.
132 'Mother's perception of the baby's birth size' is routinely used as a proxy indicator of
133 birthweight. For our analysis, we defined 'small birth size' as the birth size of an infant which
134 was perceived as either 'very small' or 'smaller than average'. Each of the outcome variables
135 was considered dichotomous for this analysis as yes (1) or no (0).

136 **Exposure variable**

137 The main exposure variable used in our analysis was the length of the preceding birth interval
138 as a measure of birth spacing. This was measured as the number of months between two
139 successive live births.^{9 15} We followed Rutstein's recommendation regarding optimal birth
140 interval of 36-59 months for our analysis.⁹ We categorised preceding birth interval in months
141 as short (<36 months) or long (\geq 60 months) birth intervals for our analysis; where the birth
142 interval of 36-59 months was the reference category.

143 **Covariates**

144 Covariates included maternal age at childbirth (19 years or below, 20-34 years and 35 years
145 or more), maternal education (none, primary and secondary or higher), birth order (2-3, ≥ 4),
146 maternal Body Mass Index (BMI) (underweight, average, overweight and obese), area of
147 residence (urban and rural), wealth index (poorest quintile, second quintile, middle quintile,
148 fourth quintile and richest quintile), maternal employment status during survey (currently
149 working and not working), maternal desire of pregnancy (yes and no), ever use of
150 contraception (yes and no), number of Antenatal Care (ANC) visits (none, 1-3 visits and ≥ 4
151 visits), ANC by Skilled Birth Attendants (SBA) (yes and no), history of any previous loss of
152 pregnancy (yes and no), sex of baby (female and male) and region (Dhaka, Barisal,
153 Chittagong, Khulna, Rajshahi, Rangpur and Sylhet).

154 We constructed the wealth index variable using principle component analysis through
155 ranking the available wealth variables in the pooled BDHS dataset such as housing materials,
156 type of toilet facility, source of drinking water, type of cooking fuel, availability of
157 electricity, ownership of assets (radio, television, fridge etc.), adjusted for urban-rural
158 differences. We constructed the 'ever use of contraception' variable from calendar data of
159 women's dataset for each year, where ever use of contraception was recorded if there was any
160 contraceptive practice at anytime.

161 **Data analysis**

162 The 'first-day neonatal mortality' and 'early neonatal mortality' variables were calculated
163 from the birth history data, where age at death was recorded in days if they were less than 30
164 days old. 'Small birth size' was calculated from the birth history data, based on the
165 perceptions of mothers about their infant's birth size. Frequencies with weighted percentage
166 were calculated for the selected variables to describe the characteristics of the women who
167 had a 'first-day neonatal death', an 'early neonatal death' and a 'small birth size' infant. We

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3 168 conducted bivariate analysis to ascertain the unadjusted association between each of the
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5 169 independent variables and each outcome separately, and multivariable analysis was
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7 170 performed to obtain the adjusted odds ratio (aOR). All covariates associated with each of
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9 171 outcomes at the p value ≤ 0.25 in unadjusted analysis were included in the final model of
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11 172 multivariable logistic regression. Also, some other covariates (maternal education, maternal
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13 173 wealth status, maternal area of residence, maternal desire of pregnancy, number of ANC and
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15 174 ANC by SBA) were included in the final model regardless of their significant levels because
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17 175 of being known risk factors of adverse pregnancy outcomes based on several previous
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19 176 literature.^{9 16 17 18} We also checked the variables for multicollinearity. The wald test was used
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21 177 to assess statistical significance with 95% confidential intervals (CI). The association was
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23 178 adjusted for potential confounders including maternal age at childbirth, birth order, maternal
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25 179 education, maternal wealth index, maternal employment status, area of residence, maternal
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27 180 BMI, maternal desire of pregnancy, ever use of contraceptive method, number of ANC visits,
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29 181 ANC by SBA, history of any previous pregnancy loss, sex of infant and region. We also
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31 182 restricted our analysis by 'history of any previous pregnancy loss' to assess the combined
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33 183 effect of history of any previous pregnancy loss and birth interval (short or long) on all three
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35 184 outcomes. We followed the direct life table approach to calculate first-day and early neonatal
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37 185 mortality rates per 1000 live births. All analyses were carried out using STATA version 14.2.
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39 186 We used the 'svy' command in all our analyses to calculate the weighted values in order to
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41 187 adjust for the clustering effect and sample stratification.

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47 188 We obtained permission from Monitoring and Evaluation to Assess and Use Results
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49 189 Demographic and Health Surveys (MEASURE DHS) to download the data from the DHS
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51 190 online archive. Ethics approval was not required for our analyses', as the data were
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53 191 anonymous and publicly available.

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3 192 **Patient involvement**

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5 193 No patients were involved in this study.
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8 194 **Figure 1: Flow diagram showing sample selection for first-day neonatal mortality, early**
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10 195 **neonatal mortality and small birth size analysis**

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13 196 **RESULTS**

14
15 197 Over the six surveys, and approximately 18 years of data, a total of 42,718 live births were
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17 198 recorded who were born to the mothers aged 15-49 years within the five years preceding the
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19 199 surveys with a high response (approximately 98%) (Figure 1). From the year 1996 to 2014,
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21 200 there was a substantial decrease in the rate of overall early neonatal mortality (30.5 vs. 23.3
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23 201 deaths per 1000 live births), but in terms of first-day neonatal mortality, we did not find any
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25 202 consistent decrease, rather the rate has increased from 9.3 deaths in 1996 to 10.6 deaths in
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27 203 2014 per 1000 live births (Figure 2). Rates of all three adverse pregnancy outcomes were
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29 204 highest among the first-born infants followed by the infants whose births were spaced less
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31 205 than 36 months (Figure 3).
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35 206 There were 33, 973 singleton live-born infants, most recently born to the mothers within the
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37 207 five years preceding each survey. Of those, 10,722 (32%) were first-born infants who were
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39 208 ineligible as there was no birth interval, which left 21,382 non-first singleton live-born
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41 209 infants in our final analysis for first-day and early neonatal mortality. For small birth size, our
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43 210 analysis consisted of 11,022 singleton live-born children, for the years 1999-2000, 2011 and
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45 211 2014, as the information regarding small birth size was not available for the surveys in 1996-
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47 212 1997, 2004 and 2007 (Figure 1).
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51 213 Of the 21,382 non-first singleton most recently live-born infants of six surveys, there were
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53 214 115 first-day and 274 early neonatal deaths. Of 11,022 non-first singleton most recently live-
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55 215 born infants of three surveys, there were 2002 infants with a birth size smaller than average.
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3 216 **Figure 2: Trends in first-day and early neonatal mortality by year of survey (1996-2014)**

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6 217 **Figure 3: First-day neonatal mortality, early neonatal mortality rates per 1000 live**
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8 218 **births and the proportion of small birth size by preceding birth intervals**

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11 219 **First-day neonatal mortality**

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13 220 Nearly half of the infants who died on the first-day (n=49) were born following a short birth
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15 221 interval, another 44 infants who died on day '0' (36.0%) were born following a long birth
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17 222 interval. Overall, mothers of the infants who died on the day '0' were more frequently aged
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19 223 between 20 and 34 years (67.5%, n=82), did not have any formal education (36.4%, n=40),
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21 224 had a parity 2-3 (63.3%, n=73), had an average BMI (59.2%, n=67) and lived in a rural area
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23 225 (79.2%, n=80) (64.1%, n=74) (Table 1).

24
25
26 226 **Early neonatal mortality**

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28 227 A large proportion of deaths in the early neonatal period was attributable to day '0' deaths
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30 228 (42.8%, n=115). Approximately 45% of infants (n=122) who died within 7 days of birth were
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32 229 born following a short birth interval. Also, a relatively higher proportion (29% vs. 26%) of
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34 230 early neonatal deaths had a long birth interval compared to the recommended birth interval
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36 231 (36-59 months). The socio-demographic characteristics of the mothers of the infants who
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38 232 died in the early neonatal period was quite similar to the day '0' findings, and the proportion
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40 233 of early neonatal mortality was highest among infants born to mothers aged 20-34 years
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42 234 (71.5%, n=200), had a parity 2-3 (60.0%, n=163), did not have any formal education (42.0%,
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44 235 n=116), lived in a rural area (81.0%, n=193), had an average BMI (58.4%, n=156) and did
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46 236 not have any ANC (55.2%, n=146) (Table 1).

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51 237 **Small birth size**

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53 238 More than one-third of infants with a small birth size (34.6%, n=698) were born with a short
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55 239 birth interval. A similar proportion of infants with a small birth size (34.2%, n=694) were

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3 240 born with a long birth interval. The highest proportion of infants perceived as small birth size
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5 241 were born to the mothers aged 20-34 years (80.0%, n=1599), had a parity 2-3 (65.8%,
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7 242 n=1322), had no formal education (38.3%, n=751), had an average BMI (54.4%, n=1069),
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9 243 lived in rural area (79.9%, n=1445) and did not have any ANC (51.4%, n=998) (Table 1).

11 244 **Association of birth intervals with first-day neonatal mortality**

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14 245 In the multivariable analysis, both short and long birth intervals were associated with the
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16 246 increased odds of first-day neonatal death. Compared to infants born following a birth
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18 247 interval of 36-59 months, infants with a short birth interval were 2.11 times more likely to die
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20 248 within 24 hours of life (95% CI: 1.17, 3.78). We also found that infants born after a long birth
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22 249 interval, compared to those born following a birth interval of 36-59 months had a 2.02 times
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24 250 higher odds of dying within 24 hours of life (95% CI: 1.10, 3.73) (Table 2).

25 251 **Association of birth intervals with early neonatal mortality**

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28 252 After adjustment for potential confounders, early neonatal mortality was associated with a
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30 253 short birth interval, while for long birth intervals there was no association. Compared to the
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32 254 infants with a birth interval of 36-59 months, infants born with a short birth interval had 1.58
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34 255 times higher odds of dying within 7 days of life (95% CI: 1.13, 2.22). Though the odds of
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36 256 early neonatal mortality were greater for long birth intervals compared to the reference group,
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38 257 there was no association (aOR: 1.23, 95% CI: 0.84, 1.81) (Table 2).

39 258 **Association of birth intervals with small birth size**

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42 259 Long birth intervals appeared to be associated with the increased odds of small birth size
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44 260 compared to the reference birth interval (aOR: 1.17, 95% CI: 1.02, 1.34), while for short birth
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46 261 intervals, the odds of small birth size were smaller (aOR: 1.04, 95% CI: 0.89, 1.20) compared
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48 262 to the reference birth interval (Table 2).

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3 263 A history of pregnancy loss can be a determinant of birth interval and we therefore restricted
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5 264 our analysis to the children whose mothers had a history of any previous pregnancy loss for
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7 265 all three outcomes. However, we found no relationship for either short or long birth intervals
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9 266 with all three outcomes, though for both short and long birth intervals there was an increase
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11 267 in the odds for first-day and early neonatal death (Table 3).
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14 268 **DISCUSSION**

15
16 269 This study suggests that both short and long birth intervals were associated with the increased
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18 270 odds of adverse pregnancy outcomes. Over the six surveys, a major proportion of infants who
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20 271 died on the first-day, or in the first week or with a small birth size were born before the
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22 272 recommended optimal period of birth interval (36–59 months). We found that a birth-to-birth
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24 273 interval shorter than 36 months was associated with an increased odds of multiple adverse
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26 274 pregnancy outcomes including first-day neonatal mortality and early neonatal mortality. Also,
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28 275 a birth-to-birth interval longer than 59 months was associated with an increased odds of first-
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30 276 day neonatal mortality and small birth size.
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34 277 Infants born with a short birth-to-birth interval of less than 36 months were associated with
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36 278 higher odds of first-day neonatal mortality. Several studies have reported the association of a
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38 279 short birth interval with perinatal or neonatal mortality.^{19 20} However, to the best of our
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40 280 knowledge, no prior research has examined the effect of birth interval on first-day neonatal
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42 281 mortality individually. Further, we found that the odds of early neonatal mortality were also
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44 282 greater among infants who were born following a short birth interval. This is consistent with
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46 283 the findings of a few earlier investigations from LMIC's which examined the effect of short
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48 284 birth intervals on perinatal, early neonatal or neonatal mortality.^{19 20} Similar to our findings, a
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50 285 previous study conducted in India reported an association of neonatal death with a birth
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52 286 interval of less than 36 months (aOR: 1.78, 95% CI: 1.63, 1.94), compared to births spaced
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54 287 36–59 months.²⁰ Again, an analysis of 47 Demographic Health Surveys from LMIC also
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3 288 supports our finding of higher odds of early neonatal mortality for short birth intervals,
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5 289 though this analysis has used a slightly different definition of both short (<24 months) and the
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7 290 reference category birth interval (24-<60 months).²¹ Also, our finding is in line with the
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9 291 finding of a previous study conducted in Matlab, Bangladesh, where they reported an
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11 292 increased risk of very short birth intervals (less than 15 months) on early neonatal mortality
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13 293 compared to those born after 36-59 months, though in their study the risk of early neonatal
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15 294 mortality goes down as the birth interval increases up to a minimum of 24-59 months, which
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17 295 is not consistent with our findings.¹² Furthermore, we did not find any significant association
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19 296 between short birth interval and small birth size, although infants born following a short
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21 297 interval were at increased odds of being born with a small birth size. In the BDHS,
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23 298 birthweight is not routinely collected and birth size is based on maternal perception which
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25 299 could lead to some errors in the estimation of small birth size and may be responsible for this
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27 300 non-association. However, the direction of the effect is consistent with several earlier
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29 301 investigations including a meta-analysis of 69 studies from both developing and developed
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31 302 countries.^{4 19 22}

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36 303 Several hypotheses have been proposed to explain the association of short birth interval on
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38 304 adverse pregnancy outcomes.²³ One of the most frequently used hypotheses is the maternal
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40 305 nutritional depletion phenomenon, which has been defined by Winkvist et al. as a negative
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42 306 change in maternal nutritional status during a reproductive cycle, mostly due to the biological
43
44 307 competition between mother and the growing fetus.²⁴⁻²⁶ Short birth spacing does not allow
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46 308 mothers sufficient time to restore nutritional reserves needed to support fetal growth and
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48 309 development during the subsequent pregnancy. This eventually causes maternal nutritional
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50 310 depletion that leads to the increase risk of adverse pregnancy outcomes among the births
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52 311 spaced after a short interval. Another explanation is that the association of short birth
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54 312 intervals and adverse pregnancy outcomes could be confounded by other factors including
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3 313 young maternal age, lower socio-economic status and lower utilisation of health services.^{27 28}

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5 314 In our analysis, after adjusting for maternal age, socio-economic factors, and maternal
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7 315 characteristics as well as health service related factors, short birth interval remained
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9 316 associated with first-day and early neonatal mortality which is in line with other studies from
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11 317 both LMIC and high income countries which controlled for similar variables.^{12 15 29 30}

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14 318 Our study further identified the association of long birth interval with adverse perinatal
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16 319 outcomes and found that infants born after a long birth interval were associated with greater
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18 320 odds of first-day neonatal mortality. The effect of long birth interval for early neonatal
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20 321 mortality was also greater but was not significant. There are only a few published studies on
21
22 322 the effect of a long birth interval on adverse pregnancy outcome in LMIC and the results are
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24 323 conflicting.^{4 19 20} In contrast to our findings, a previous investigation conducted in India,
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26 324 which examined the effect for long birth interval for perinatal death, did not find any
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28 325 association,¹⁹ and a pooled analysis of 47 Demographic Health Surveys examined the effect
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30 326 of longer interval for neonatal mortality and found that the odds were lower for the longer
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32 327 preceding birth intervals (≥ 60 months) (OR: 0.80, 95% CI: 0.67, 0.95) compared to the birth
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34 328 interval of 24-<60 months.²¹ The inconsistency in findings could be attributed to
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36 329 methodological differences in both the reference category (36-59 months vs. 24-<60 months)
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38 330 of the main exposure variable and the difference in the outcome variable (early neonatal
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40 331 mortality vs. neonatal mortality). However, our findings are consistent with a meta-analysis
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42 332 which reported higher odds of early neonatal mortality with a longer interval,⁴ and Rutstein's
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44 333 study which analysed data from 17 developing countries with the same finding.⁹ Again, we
45
46 334 found that a long birth interval was associated with a greater odds of small birth size. This is
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48 335 similar to a few prior studies which also reported the detrimental effect of a long birth
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50 336 interval on birth size.^{4 19 31}

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3 337 The increased odds of adverse pregnancy outcomes for long birth intervals may be due to
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5 338 some concurrent factors such as advanced maternal age and previous history of pregnancy
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7 339 loss. In an earlier investigation, Zhu et al. explained the association between long birth
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9 340 intervals and adverse pregnancy outcomes through the gradual decline in the maternal
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11 341 physiological and anatomical capacities of the reproductive system, hypothesising that if a
12
13 342 woman does not conceive for an extended time after a delivery, her physiological
14
15 343 characteristics may return to her primigravid state.³²
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18 344 **Strengths and limitations**

19
20 345 The main strength of our study is that it was based on a large nationally representative sample
21
22 346 from six surveys within an 18-year time period in a single country which would improve the
23
24 347 homogeneity of the data. We restricted our analysis to the most recent live births within the
25
26 348 five years prior to the interview date to minimise recall bias. Furthermore, we were able to
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28 349 add a number of potential confounding factors.
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30

31 350 We acknowledge some methodological limitations. First, this is a cross-sectional data, which
32
33 351 may limit the identification of a causal relationship between the birth interval and adverse
34
35 352 pregnancy outcomes. Secondly, BDHS data relies on maternal recall and report of the
36
37 353 information regarding preceding birth intervals and the days of infant deaths, which is subject
38
39 354 to recall bias. Third, there is a possibility of underreporting of infant deaths, as birth histories
40
41 355 and infant survival information were only collected from surviving mothers and there is a
42
43 356 strong association between maternal and infant deaths. Fourth, we acknowledge a limitation
44
45 357 of using maternal perception on birth size instead of birthweight in our analysis due to
46
47 358 unavailability of actual estimates of birthweight in BDHS, which may reflect newborn's
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49 359 overall health status rather than birthweight only. Fifth, as we pooled six BDHS datasets over
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51 360 18 years, there may be a possibility of changes in the background characteristics of the
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53 361 population over 18 years. Also, in our analysis, we were unable to include the variable
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3 362 regarding the history of immediate previous adverse outcome such as stillbirth, miscarriage
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5 363 etc. which is a major determinant of adverse perinatal outcomes in the subsequent pregnancy.
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7 364 A previous investigation conducted in Bangladesh using dynamic panel data models, reported
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9 365 that a previous adverse birth outcome may be subject to ‘scarring effect’ which leads to a
10
11 366 short birth interval (replacement) and thus increases the risk of mortality of the subsequent
12
13 367 infant (nutritional depletion); as a mother with a previous pregnancy loss may rush into a
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15 368 pregnancy without properly recovering from the pregnancy loss.³³ In our analysis, we were
16
17 369 unable to consider the role of ‘scarring effect’ related to a previous adverse pregnancy
18
19 370 outcome which has an influence on birth interval. However, we were able to include the
20
21 371 variable ‘ever had a pregnancy loss’ in our analysis, but none of our outcome variables was
22
23 372 significant, though stratifying by that variable increased the effect sizes of first-day and early
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25 373 neonatal mortality for both short and long birth intervals.
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374 **CONCLUSIONS**

375 Our analysis supports the reduced risk of adverse pregnancy outcomes following a birth-to-
376 birth interval of 36-59 months which is consistent with the WHO recommendation of a birth-
377 to-pregnancy interval of 24 months. Our results highlight several important implications for
378 care-providers, program managers and policymakers by suggesting that a preceding birth
379 interval of 36-59 months could prevent adverse pregnancy outcomes including first-day
380 neonatal death, early neonatal death and low birthweight. Promoting an optimal birth interval
381 of 36-59 months in postpartum family planning is needed.

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4
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12
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15
16
17 388 **Authors' contributions**

18
19 389 MKN, CRG and AA conceptualised and designed the study. MKN performed the literature
20
21 390 review. MKN, CRG, MTI and TH performed statistical analysis. MKN and CRG drafted the
22
23 391 manuscript. MKN and CRG contributed to the interpretation of the data. MKN, CRG, AA
24
25 392 and MTI contributed to the critical revision of the manuscript. All the authors read and
26
27 393 approved the final manuscript.

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30
31 394 **Conflict of interest**

32
33 395 We declare that we have no conflict of interest.

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35
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39
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42
43 399 **Data sharing statement**

44
45 400 The data are anonymous and publicly available in the website; www.measuredhs.com.

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Table 1: First-day neonatal mortality, early neonatal mortality and small birth size infants by maternal characteristics in Bangladesh: BDHS 1996-2014

Predictors	First-day neonatal mortality (N= 21,382) n (%) n=115	Early neonatal mortality (N= 21,382) n (%) n=274	Small birth size (N= 11,022) n (%) n=2,002
Preceding birth interval in months			
<36 months	49 (45.2)	122 (45.2)	698 (34.6)
36-59 months	22 (18.8)	70 (26.2)	610 (31.2)
≥ 60 months	44 (36.0)	82 (28.6)	694 (34.2)
Mother's age at childbirth			
≤19 years	20 (21.1)	40 (16.2)	218 (10.7)
20-34 years	82 (67.5)	200 (71.5)	1599 (80.0)
≥35 years	13 (11.4)	34 (12.3)	185 (9.3)
Birth order			
2-3	73 (63.3)	163 (60.0)	1322 (65.8)
≥4	42 (36.7)	111 (40.0)	680 (34.2)
Maternal education			
None	40 (36.4)	116 (42.0)	751 (38.3)
Primary	41 (33.7)	84 (30.6)	618 (29.0)
Secondary or higher	34 (29.9)	74 (27.4)	633 (32.7)
Wealth index			
Poorest quintile	24 (19.6)	71 (23.5)	428 (19.6)
Second quintile	24 (21.6)	63 (24.0)	394 (19.8)
Middle quintile	24 (19.5)	57 (22.2)	389 (19.4)
Fourth quintile	20 (20.2)	35 (13.5)	388 (20.7)
Richest quintile	23 (19.1)	48 (16.8)	403 (20.5)
Employment status			
Currently working	34 (32.1)	70 (28.0)	339 (18.0)
Not working	81 (67.9)	204 (72.0)	1663 (82.0)
Area of residence			
Urban	35 (20.8)	81 (19.0)	557 (20.1)
Rural	80 (79.2)	193 (81.0)	1445 (79.9)
Maternal BMI			
Underweight	27 (23.1)	83 (29.3)	711 (35.3)
Average	67 (59.2)	156 (58.4)	1069 (54.5)
Overweight	16 (13.1)	26 (9.3)	169 (7.9)
Obese	5 (4.6)	9 (3.0)	53 (2.3)
Maternal desire of			

pregnancy			
Yes	77 (63.3)	171 (63.5)	1205 (60.1)
No	38 (36.7)	103 (36.5)	797 (39.9)
Ever use of contraception			
Yes	81 (72.9)	196 (71.9)	1605 (81.1)
No	34 (27.1)	78 (28.1)	397 (18.9)
No. of ANC visits			
None	48 (43.1)	146 (55.2)	998 (51.4)
1-3 visits	46 (40.7)	90 (32.0)	683 (33.7)
≥4 visits	21 (16.2)	38 (12.8)	321 (14.9)
ANC by SBA			
Yes	56 (47.3)	111 (38.6)	817 (38.8)
No	59 (52.7)	163 (61.4)	1185 (61.2)
History of any previous pregnancy loss			
Yes	35 (26.3)	79 (26.2)	435 (21.4)
No	80 (73.7)	195 (73.8)	1567 (78.6)
Sex of infant			
Male	74 (64.1)	162 (58.0)	943 (44.9)
Female	41 (35.9)	112 (42.0)	1059 (55.1)
Region			
Barisal	10 (4.2)	28 (5.5)	176 (4.7)
Chittagong	12 (10.1)	40 (13.9)	463 (25.4)
Khulna	10 (8.2)	27 (9.0)	232 (8.6)
Rajshahi	27 (25.1)	50 (20.9)	227 (13.2)
Rangpur	15 (8.0)	47 (10.7)	235 (8.2)
Sylhet	10 (3.5)	18 (3.5)	281 (7.1)
Dhaka	31 (40.9)	64 (36.5)	388 (32.8)
Year of survey			
1996	16 (14.0)	45 (15.8)	-
1999	13 (10.7)	45 (15.8)	705 (34.2)
2004	22 (20.1)	55 (21.2)	-
2007	19 (17.9)	37 (13.6)	-
2011	29 (24.1)	59 (21.5)	813 (40.1)
2014	16 (13.2)	33 (12.1)	484 (25.7)

Table 2: Results of multivariable analysis for the association between preceding birth intervals and adverse pregnancy outcomes in Bangladesh:

BDHS 1996-2014

Predictors	First-day neonatal mortality N=21,382		Early neonatal mortality N=21,382		Small birth size N=11,022	
	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Preceding birth interval in months						
<36 months	2.11 (1.17, 3.78)	<0.05	1.58 (1.13, 2.22)	<0.05	1.04 (0.90, 1.20)	0.08
36-59 months	Reference		Reference		Reference	
≥60 months	2.02 (1.10, 3.73)		1.23 (0.84, 1.81)		1.17 (1.02, 1.34)	
Mother's age at childbirth						
≤19 years	2.51 (1.35, 4.66)	<0.05	1.53 (1.02, 2.28)	<0.05	1.01 (0.83, 1.21)	0.68
20-34 years	Reference		Reference		Reference	
≥35 years	1.34 (0.67, 2.69)		1.46 (0.93, 2.29)		1.10 (0.89, 1.36)	
Birth order						
2-3	Reference		Reference		Reference	
≥4	1.48 (0.88, 2.50)	0.14	1.27 (0.92, 1.75)	0.15	1.02 (0.89, 1.16)	0.81
Maternal education						
None	0.97 (0.49, 1.94)	0.80	0.94 (0.60, 1.46)	0.94	1.09 (0.91, 1.30)	0.05
Primary	1.15 (0.62, 2.11)		0.98 (0.65, 1.50)		0.91 (0.77, 1.07)	
Secondary or higher	Reference		Reference		Reference	
Wealth status						
Poorest quintile	0.76 (0.34, 1.68)	0.89	0.86 (0.53, 1.40)	0.68	1.30 (1.05, 1.61)	<0.05
Second quintile	0.92 (0.43, 1.95)		0.99 (0.61, 1.63)		1.34 (1.09, 1.64)	
Middle quintile	0.97 (0.48, 1.96)		1.09 (0.70, 1.72)		1.12 (0.91, 1.37)	
Fourth quintile	1.15 (0.58, 2.28)		0.80 (0.48, 1.32)		1.12 (0.93, 1.37)	

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5	Richest quintile	Reference		Reference		Reference	
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7	Employment status						
8	Currently working	1.59 (0.99, 2.56)	0.05	1.30 (0.96, 1.75)	0.09	1.02 (0.87, 1.19)	0.83
9	Not working	Reference		Reference		Reference	
10							
11	Area of residence						
12	Urban	1.10 (0.64, 1.88)	0.72	1.14 (0.80, 1.63)	0.46	1.09 (0.93, 1.27)	0.28
13	Rural	Reference		Reference		Reference	
14							
15	Maternal BMI						
16	Underweight	0.58 (0.35, 0.97)	<0.05	0.70 (0.52, 0.94)	0.05	1.19 (1.05, 1.34)	<0.05
17	Average	Reference		Reference		Reference	
18	Overweight	1.81 (0.90, 3.65)		1.36 (0.80, 2.32)		0.86 (0.70, 1.07)	
19	Obese	1.84 (0.59, 5.67)		1.23 (0.53, 2.89)		0.86 (0.60, 1.23)	
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22	Maternal desire of						
23	pregnancy						
24	Yes	1.09 (0.71, 1.68)	0.68	1.13 (0.84, 1.51)	0.43	0.92 (0.81, 1.05)	0.22
25	No	Reference		Reference		Reference	
26							
27	Ever use of contraception						
28	Yes	Reference		Reference		Reference	
29	No	2.20 (1.32, 3.68)	<0.05	1.89 (1.35, 2.64)	<0.001	1.23 (1.06, 1.42)	<0.05
30							
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32	No of ANC visits						
33	None	0.89 (0.29, 2.73)	0.62	1.61 (0.74, 3.48)	0.48	1.09 (0.84, 1.42)	0.79
34	1-3 visits	1.21 (0.61, 2.37)		1.16 (0.71, 1.89)		1.03 (0.86, 1.23)	
35	≥4 visits	Reference		Reference		Reference	
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37	ANC by SBA						
38	Yes	Reference		Reference		Reference	
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No	1.01 (0.46, 2.19)	0.99	0.78 (0.43, 1.42)	0.42	1.05 (0.83, 1.32)	0.70
History of any previous pregnancy loss						
Yes	1.31 (0.85, 2.03)	0.22	1.27 (0.94, 1.71)	0.12	1.04 (0.91, 1.20)	0.53
No	Reference		Reference		Reference	
Sex of infant						
Male	1.70 (1.09, 2.64)	<0.05	1.32 (1.01, 1.73)	<0.05	0.71 (0.63, 0.80)	<0.001
Female	Reference		Reference		Reference	
Region						
Barisal	0.59 (0.27, 1.30)	<0.05	0.82 (0.51, 1.30)	<0.05	0.74 (0.59, 0.92)	<0.001
Chittagong	0.34 (0.16, 0.71)		0.50 (0.32, 0.77)		1.16 (0.97, 1.38)	
Khulna	0.72 (0.35, 1.50)		0.91 (0.57, 1.44)		0.96 (0.79, 1.17)	
Rajshahi	1.12 (0.63, 1.99)		1.02 (0.68, 1.53)		0.73 (0.60, 0.89)	
Rangpur	0.68 (0.35, 1.29)		0.99 (0.66, 1.51)		0.81 (0.65, 0.99)	
Sylhet	0.83 (0.36, 1.88)		0.92 (0.53, 1.61)		1.24 (1.03, 1.50)	
Dhaka	Reference		Reference		Reference	

*Odds ratios were adjusted for maternal age at childbirth, birth order, maternal education, maternal wealth index, maternal employment status, area of residence, maternal BMI, maternal desire of pregnancy, ever use of contraceptive method, number of ANC visits, ANC by SBA, history of any previous pregnancy loss, sex of infant and region

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Table 3: Results of multivariable analysis for the association between preceding birth intervals and adverse pregnancy outcomes by history of any previous pregnancy loss: BDHS 1996-2014

Predictors	First-day neonatal mortality N=21,382		Early neonatal mortality N=21,382		Small birth size N=11,022	
	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Preceding birth interval in months*history of any previous pregnancy loss						
<36 months	2.12 (0.74, 6.13)	0.28	1.77 (0.90, 3.49)	0.19	0.96 (0.69, 1.33)	0.38
36-59 months	Reference		Reference		Reference	
≥60 months	2.15 (0.73, 6.31)		1.74 (0.84, 3.62)		1.18 (0.87, 1.59)	

*Odds ratios were adjusted for maternal age at childbirth, birth order, maternal education, maternal wealth index, maternal employment status, area of residence, maternal BMI, maternal desire of pregnancy, ever use of contraceptive method, number of ANC visits, ANC by SBA, sex of infant and region

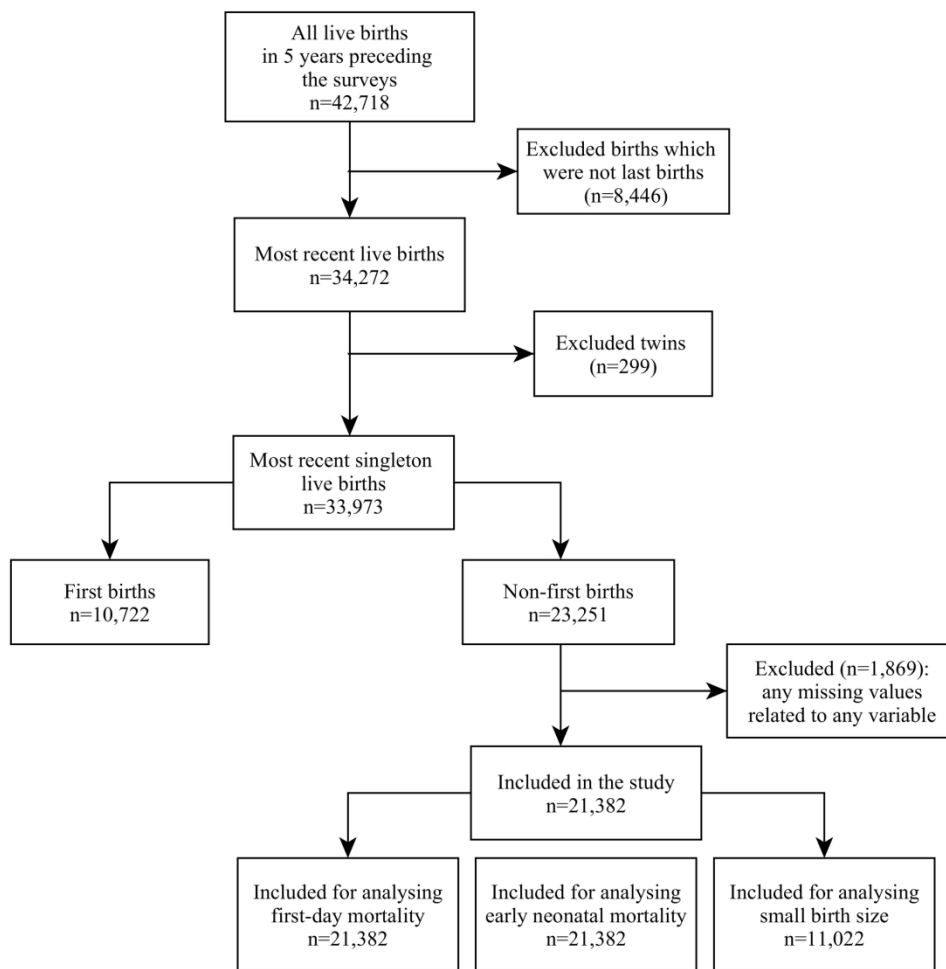


Figure 1: Flow diagram showing sample selection for first-day neonatal mortality, early neonatal mortality and small birth size analysis

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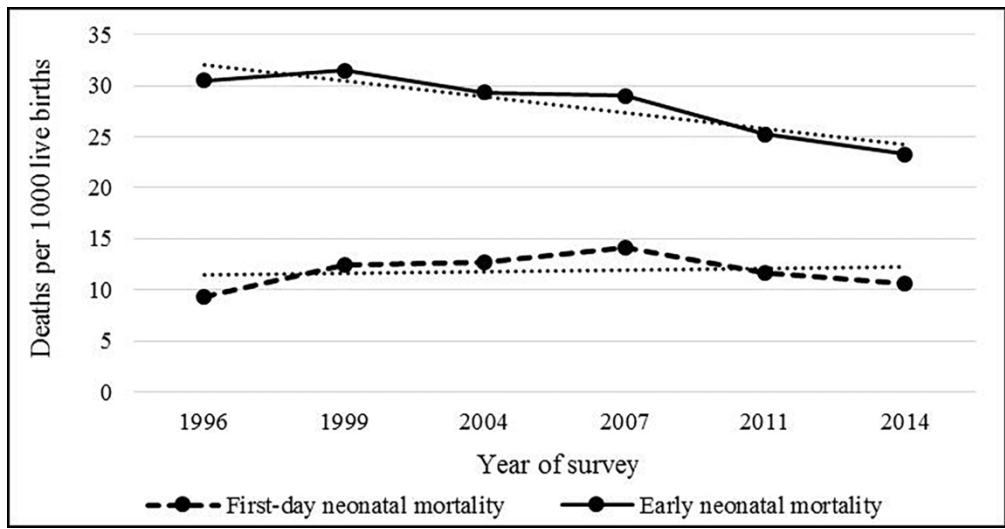


Figure 2: Trends in first-day and early neonatal mortality by year of survey (1996-2014)

191x99mm (300 x 300 DPI)

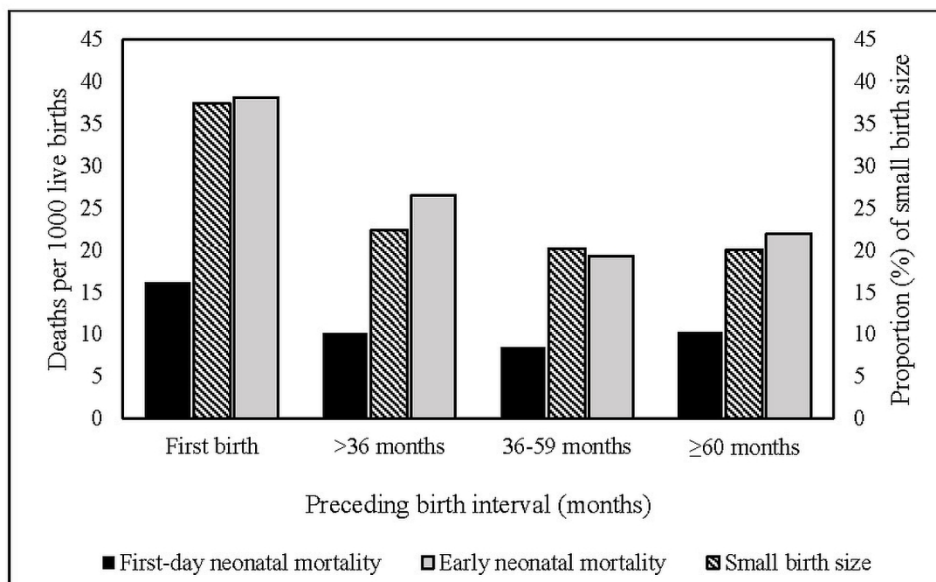


Figure 3: First-day neonatal mortality, early neonatal mortality rates per 1000 live births and the proportion of small birth size by preceding birth intervals

149x101mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*:
 Manuscript ID bmjopen-2018-024392

	Item No	Recommendation	Reported on page no.
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 2, line 31
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2, line 30-38, 41-49
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5, line 71-99
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5, line 99-104
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5-6, line 107-124
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5-6, line 107-124
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Page 6, line 122-124
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7, line 125-160
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	Page 6, line 125-135
Bias	9	Describe any efforts to address potential sources of bias	Page 6, line 122-124
Study size	10	Explain how the study size was arrived at	Page 5-6, line 107-124, Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7-8, line 162-186
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 7-8, line 162-187
		(b) Describe any methods used to examine subgroups and interactions	Page 8, line 181-183
		(c) Explain how missing data were addressed	Figure 1
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	Page 8, line 181-183
Results			
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	Figure 1, Page 9, line 197-215

		follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Page 9, line 206-212
		(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	Table 1, Page 10-11, line 219-243
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures	Table 1
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	Table 2
		(b) Report category boundaries when continuous variables were categorized	Page 7, line 144-146, 150
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12, line 269-276
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	Page 15, line 348-371
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12-15, line 269-341
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 16, line 373-379
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	N/A

BMJ Open

Risk of adverse pregnancy outcomes associated with short and long birth intervals in Bangladesh: evidence from six Bangladesh Demographic and Health Surveys, 1996-2014

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Keywords:	First-day neonatal death, Early neonatal death, Small birth size, Pregnancy outcome, Birth interval, Bangladesh

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3 1 **Risk of adverse pregnancy outcomes associated with short and long birth intervals in**
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5 2 **Bangladesh: evidence from six Bangladesh Demographic and Health Surveys, 1996-**
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7 3 **2014**
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55 23 acknowledgement, author's contribution, conflict of interest, funding statement, data sharing
56

57 24 statement, tables and figures)
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60 25

26 ABSTRACT

27 Objective

28 To examine the effect of short (<36 months) and long (≥ 60 months) birth intervals on adverse
29 pregnancy outcomes in Bangladesh.

30 Design, setting and participants

31 We analysed data from six Bangladesh Demographic and Health Surveys (1996-1997, 1999-
32 2000, 2004, 2007, 2011 and 2014). We included all singleton non-first live births, most recently
33 born to mothers within five years preceding each survey (n=21,382). We defined birth interval
34 according to previous research which suggests that a birth interval between 36 and 59 months
35 is the most ideal interval. Bivariate and multivariable analyses were conducted to obtain the
36 crude and adjusted odds ratios (aOR) respectively to assess the odds of first-day neonatal death,
37 early neonatal death and small birth size for both short (<36 months) and long (≥ 60 months)
38 spacing between births.

39 Main outcome measures

40 First-day neonatal death, early neonatal death and small birth size.

41 Results

42 In the multivariable analysis, compared to births spaced 36-59 months, infants with a birth
43 interval of less than 36 months had increased odds of first-day neonatal death (aOR: 2.11, 95%
44 CI: 1.17, 3.78) and early neonatal death (aOR: 1.58, 95% CI: 1.13, 2.22). Compared to births
45 spaced 36-59 months, infants with a birth interval of ≥ 60 months, had increased odds of first-
46 day neonatal death (aOR: 2.02, 95% CI: 1.10, 3.73) and small birth size (aOR: 1.17, 95% CI:
47 1.02, 1.34). When there was a history of any previous pregnancy loss, there was an increase in
48 the odds of first-day and early neonatal death for both short and long birth intervals, although
49 it was not significant.

50 **Conclusions**

51 Birth intervals shorter than 36 months and longer than 59 months are associated with increased
52 odds of adverse pregnancy outcomes. Care-providers, program managers and policymakers
53 could focus on promoting an optimal birth interval between 36-59 months in postpartum family
54 planning.

55 **Key words:** Pregnancy outcome, birth interval, first-day neonatal death, early neonatal death,
56 small birth size, Bangladesh

58 **Strengths and limitations of this study**

- 59 • The main strength of this study is the use of a large sample from six nationally
60 representative surveys of Bangladesh with a very high response (98%).
- 61 • We used data from most recent births within the 5 years preceding the surveys in order
62 to minimise recall bias.
- 63 • Our study is the first in Bangladesh which analysed the effect of birth intervals and
64 other risk factors for first-day neonatal mortality.
- 65 • Demographic and Health Survey data is cross-sectional, which reduces the ability to
66 infer causation.
- 67 • Demographic and Health Survey data uses maternal perceptions of infant birth size as
68 a proxy for birthweight which may be a limitation.

70 **BACKGROUND**

71 Adverse pregnancy outcomes such as stillbirth, early neonatal mortality and low birthweight
72 are of considerable public health significance. Globally, perinatal mortality (stillbirth and early
73 neonatal mortality) accounts for more than 6 million deaths every year. Of those deaths,
74 approximately 2 million occur in the early neonatal period.¹ The risk is greatest on the first day
75 of life, approximately 1 million newborns die within the first 24 hours.¹ Further, low
76 birthweight, occurs in more than 20 million newborns worldwide, which is a major contributor
77 to perinatal mortality and up to 80% of neonatal mortality.² The greatest proportion of perinatal
78 deaths and low birthweight (97-99%) occur in Low and Middle-Income Countries (LMICs).³

79 Several interventions have been suggested to address adverse pregnancy outcomes, such as
80 pregnancy spacing.⁴ Both short and long birth intervals have been reported to be associated
81 with an increased risk of a number of adverse perinatal outcomes.^{5 6} Current World Health
82 Organization (WHO) guidelines recommend an interval of at least 24 months before attempting
83 the next pregnancy after a live birth (i.e. birth-to-pregnancy interval) in order to reduce any
84 adverse pregnancy outcomes.⁷ Thus, the birth-to-birth interval should be at least 33 months by
85 including nine months of pregnancy to the recommended 24 months.⁸ In an analysis of
86 Demographic and Health Survey data from 17 developing countries, Rutstein suggested that
87 the optimal birth interval should be between 36 and 59 months as birth intervals less than 36
88 and more than 59 months showed a tendency towards neonatal mortality and morbidity.⁹ The
89 WHO highlighted the necessity of future research investigating the association between birth
90 interval and adverse pregnancy outcomes.⁷

91 Bangladesh has a high perinatal mortality (44 per 1000 pregnancies) and morbidity,¹⁰ where
92 birth spacing remains a problem.¹¹ Between the year 1993 and 2014, though the median birth
93 interval increased by 49% (from 35 months to 52 months), approximately 30% of non-first

1
2
3 94 births occurred within less than 36 months (7 months to 35 months) following the previous
4
5 95 birth.¹⁰ However, another 40% of non-first births occurred following a birth interval of more
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7 96 than 59 months.¹⁰ Of the papers investigating birth interval in Bangladesh, most have focussed
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9
10 97 on the effect of a short birth interval and have not considered a long birth interval as a risk of
11
12 98 adverse perinatal outcome.^{12 13} Given the changing demographics in Bangladesh and an
13
14 99 increase in the proportion of longer birth intervals, our objective was to examine whether the
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16
17 100 preceding birth interval (short or long) was independently associated with an increased risk of
18
19 101 adverse pregnancy outcomes including first-day neonatal mortality, early neonatal mortality
20
21 102 and low birthweight, using pooled data from the Bangladesh Demographic and Health Surveys
22
23
24 103 (BDHS).

27 104 **METHODS**

29 105 **Data source**

31
32 106 We used the BDHS data from the years; 1996-1997, 1999-2000, 2004, 2007, 2011 and 2014.
33
34 107 BDHS is a nationally representative household survey carried out every three to four years
35
36 108 under the authority of the National Institute of Population Research and Training of the
37
38 109 Ministry of Health and Family Welfare. The survey employed a two-stage stratified cluster-
39
40 110 sampling design with rural and urban samples to collect information from ever-married women
41
42 111 aged 15-49 years and ever-married men 15-54 years about demographic and health status. Data
43
44 112 were obtained from the website; www.measuredhs.com. The BDHS consists of three types of
45
46 113 questionnaires: household, women, and men. Our analysis was limited to the information
47
48 114 obtained from the women's and household questionnaires. We pooled the data files from six
49
50 115 surveys and analysed the live births occurring during the five years preceding the surveys. The
51
52 116 Demographic and Health Survey program employs standardised data collection procedures
53
54 117 with model questionnaires to ensure consistent content over time and across countries allowing
55
56 118 comparability across populations cross-sectionally and over time.¹⁴ We selected six recent

1
2
3 119 surveys in this pooled analysis based on the similarities in sampling design, comparability of
4
5 120 survey questionnaires for focus variables of this analysis, and availability of data for the pooled
6
7
8 121 analysis. In our analysis, we included the data from all singleton, non-first, most recent live-
9
10 122 born children within the five years preceding the six BDHSs, 1996-1997, 1999-2000, 2004,
11
12 123 2007, 2011 and 2014.

124 **Outcome variables**

125 We conducted three analyses, with three different outcome variables - 'first-day neonatal
126 death', 'early neonatal death' and 'small birth size'. First-day deaths were defined as deaths
127 during the first 24 hours after birth (day 0) among live-born children, and early neonatal deaths
128 were deaths between the age of 0 to 6 days among live-born children. These two outcome
129 variables overlap, but conform to standard definitions. We used 'small birth size' as a proxy
130 for low birthweight. Estimates of birthweight are not collected by the BDHS. 'Mother's
131 perception of the infant's birth size is routinely used as a proxy indicator of birthweight. For
132 our analysis, we defined 'small birth size' as the birth size of an infant which was perceived as
133 either 'very small' or 'smaller than average'. Each of the outcome variables was considered
134 dichotomous for this analysis as yes (1) or no (0).

135 **Exposure variable**

136 The main exposure variable used in our analysis was the length of the preceding birth interval
137 as a measure of birth spacing. This was measured as the number of months between two
138 successive live births.^{9 15} We followed Rutstein's recommendation regarding optimal birth
139 interval of 36-59 months for our analysis.⁹ We categorised the preceding birth interval in
140 months as short (<36 months) or long (≥ 60 months) birth intervals for our analysis; where the
141 birth interval of 36-59 months was the reference category.

142 **Covariates**

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2
3 143 Covariates included maternal age at childbirth (19 years or below, 20-34 years and 35 years or
4
5 144 more), maternal education (none, primary and secondary or higher), birth order (2-3, ≥ 4),
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7 145 maternal Body Mass Index (BMI) (underweight, average, overweight and obese), area of
8
9 146 residence (urban and rural), wealth index (poorest quintile, second quintile, middle quintile,
10
11 147 fourth quintile and richest quintile), maternal employment status during survey (currently
12
13 148 working and not working), maternal desire of pregnancy (yes and no), ever use of contraception
14
15 149 (yes and no), number of Antenatal Care (ANC) visits (none, 1-3 visits and ≥ 4 visits), ANC by
16
17 150 Skilled Birth Attendants (SBA) (yes and no), history of any previous loss of pregnancy (yes
18
19 151 and no), sex of baby (female and male) and region (Dhaka, Barisal, Chittagong, Khulna,
20
21 152 Rajshahi, Rangpur and Sylhet).

22
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26
27 153 We constructed the 'wealth index' variable using principle component analysis through ranking
28
29 154 the available wealth variables in the pooled BDHS dataset such as housing materials, type of
30
31 155 toilet facility, source of drinking water, type of cooking fuel, availability of electricity,
32
33 156 ownership of assets (radio, television, fridge etc.), adjusted for urban-rural differences. We
34
35 157 constructed the 'ever use of contraception' variable from calendar data of women's dataset for
36
37 158 each year, where 'ever use of contraception' was recorded if there was any contraceptive
38
39 159 practice at anytime.

160 **Data analysis**

161 The 'first-day neonatal mortality' and 'early neonatal mortality' variables were calculated from
162 the birth history data, where age at death was recorded in days if they were less than 30 days
163 old. 'Small birth size' was calculated from the birth history data, based on the perceptions of
164 mothers about their infant's birth size. Frequencies with weighted percentage were calculated
165 for the selected variables to describe the characteristics of the women who had a 'first-day
166 neonatal death', an 'early neonatal death' and a 'small birth size' infant. We conducted
167 bivariate analysis to ascertain the unadjusted association between each of the independent

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3 168 variables and each outcome separately, and multivariable analysis was performed to obtain the
4
5 169 adjusted odds ratio (aOR). All covariates associated with the outcomes at $p \leq 0.25$ in the
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7
8 170 unadjusted analysis were included in the final multivariable logistic regression model. Further,
9
10 171 several other covariates (maternal education, maternal wealth status, maternal area of
11
12 172 residence, maternal desire of pregnancy, number of ANC and ANC by SBA) were included in
13
14 173 the final model regardless of their significant levels because they are known risk factors of
15
16 174 adverse pregnancy outcomes.^{9 16 17 18} The 'year of survey' was not included in our final model
17
18 175 as the p-value between 'year of survey' and each of the outcome variables was more than 0.25
19
20 176 in the unadjusted analysis. However, to test the effect of 'year of survey' we repeated the model
21
22 177 and included 'year of survey'. This made no difference to the findings (results not shown), and
23
24 178 hence, we kept the original model. We also checked the variables for multicollinearity. The
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26 179 Wald test was used to assess statistical significance with a 95% confidence interval (CI). The
27
28 180 association was adjusted for potential confounders including maternal age at childbirth, birth
29
30 181 order, maternal education, maternal wealth index, maternal employment status, area of
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32 182 residence, maternal BMI, maternal desire of pregnancy, ever use of contraceptive method,
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34 183 number of ANC visits, ANC by SBA, history of any previous pregnancy loss, sex of infant and
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36 184 region.

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43 185 We further restricted our analysis by 'history of any previous pregnancy loss' to assess the
44
45 186 combined effect of history of any previous pregnancy loss and birth interval (short or long) on
46
47 187 all three outcomes. We followed the direct life table approach to calculate first-day and early
48
49 188 neonatal mortality rates per 1000 live births. All analyses were carried out using STATA
50
51 189 version 14.2. We used the 'svy' command in all our analyses to calculate the weighted values
52
53 190 in order to adjust for the clustering effect and sample stratification.
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3 191 We obtained permission from Monitoring and Evaluation to Assess and Use Results
4
5 192 Demographic and Health Surveys (MEASURE DHS) to download the data from the DHS
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7
8 193 online archive. Ethics approval was not required for our analyses, as the data were anonymous
9
10 194 and publicly available.

13 195 **Patient involvement**

15
16 196 No patients were involved in this study.

19 197 **Figure 1: Flow diagram showing sample selection for first-day neonatal mortality, early** 20 21 22 198 **neonatal mortality and small birth size analysis**

25 199 **RESULTS**

27 200 Over the six surveys, and approximately 18 years of data, a total of 42,718 live births were
28
29 201 recorded who were born to mothers aged 15-49 years within the five years preceding the
30
31 202 surveys with a high response (approximately 98%) (Figure 1). From the years 1996 to 2014,
32
33 203 there was a substantial decrease in the rate of overall early neonatal mortality (30.5 vs. 23.3
34
35 204 deaths per 1000 live births), but in terms of first-day neonatal mortality, we did not find any
36
37 205 consistent decrease, rather the rate has increased from 9.3 deaths in 1996 to 10.6 deaths in 2014
38
39 206 per 1000 live births (Figure 2). Rates of all three adverse pregnancy outcomes were highest
40
41 207 among the first-born infants followed by the infants whose births were spaced less than 36
42
43 208 months (Figure 3).

47 209 There were 33, 973 singleton live-born infants, most recently born to mothers within the five
48
49 210 years preceding each survey. Of those, 10,722 (32%) were first-born infants who were
50
51 211 ineligible as there was no birth interval, which left 21,382 non-first singleton live-born infants
52
53 212 in our final analysis for first-day and early neonatal mortality. For small birth size, our analysis
54
55 213 consisted of 11,022 singleton live-born infants only, for the years 1999-2000, 2011 and 2014,
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214 as the data regarding birth size were not available for the surveys in 1996-1997, 2004 and 2007
215 (Figure 1).

216 Of the 21,382 non-first singleton most recently live-born infants of six surveys, there were 115
217 first-day and 274 early neonatal deaths. Of 11,022 non-first singleton most recently live-born
218 infants of three surveys, there were 2,002 infants with a birth size smaller than average.

219 **Figure 2: Trends in first-day and early neonatal mortality by year of survey (1996-2014)**

220 **Figure 3: First-day neonatal mortality, early neonatal mortality rates per 1000 live births
221 and the proportion of small birth size by preceding birth intervals**

222 **First-day neonatal mortality**

223 Nearly half of the infants who died on the first-day (n=49) were born following a short birth
224 interval, another 44 infants who died on day '0' (36.0%) were born following a long birth
225 interval. Overall, a greater proportion of mothers of the infants who died on day '0' aged
226 between 20-34 years (n=82, 67.5%), did not have any formal education (n=40, 36.4%), had a
227 parity 2-3 (n=73, 63.3%), had an average BMI (n=67, 59.2%) and lived in a rural area (n=80,
228 79.2%) (Table 1).

229 **Early neonatal mortality**

230 A large proportion of deaths in the early neonatal period were attributable to day '0' deaths
231 (n=115, 42.8%). Approximately 45% of infants (n=122) who died within 7 days of birth were
232 born following a short birth interval. Further, a relatively higher proportion (29% vs. 26%) of
233 early neonatal deaths had a long birth interval compared to the recommended birth interval (36-
234 59 months). The socio-demographic characteristics of mothers of the infants who died in the
235 early neonatal period were quite similar to the day '0' findings, and the proportion of early
236 neonatal mortality was highest among infants born to mothers aged 20-34 years (n=200,
237 71.5%), had a parity 2-3 (n=163, 60.0%), did not have any formal education (n=116, 42.0%),

238 lived in a rural area (n=193, 81.0%), had an average BMI (n=156, 58.4%) and did not receive
239 any ANC (n=146, 55.2%) (Table 1).

240 **Small birth size**

241 More than one-third of infants with a small birth size (n=698, 34.6%) were born with a short
242 birth interval. A similar proportion of infants with a small birth size (n=694, 34.2%) were born
243 with a long birth interval. The highest proportion of infants with a small birth size were born
244 to mothers aged 20-34 years (n=1,599, 80.0%), had a parity 2-3 (n=1,322, 65.8%), had no
245 formal education (n=751, 38.3%), had an average BMI (n=1,069, 54.5%), lived in a rural area
246 (n=1,445, 79.9%) and did not receive any ANC (n=998, 51.4%) (Table 1).

247 **Association of birth intervals with first-day neonatal mortality**

248 In the multivariable analysis, both short and long birth intervals were associated with increased
249 odds of first-day neonatal death. Compared to infants born following a birth interval of 36-59
250 months, infants with a short birth interval were 2.11 times more likely to die within 24 hours
251 of life (95% CI: 1.17, 3.78). We also found that infants born after a long birth interval,
252 compared to those born following a birth interval of 36-59 months had 2 times higher odds of
253 dying within 24 hours of life (95% CI: 1.10, 3.73) (Table 2).

254 **Association of birth intervals with early neonatal mortality**

255 After adjustment for potential confounders, early neonatal mortality was associated with a short
256 birth interval, while for long birth intervals, no significant association was found. Compared to
257 infants with a birth interval of 36-59 months, infants born with a short birth interval had 1.58
258 times higher odds of dying within 7 days of life (95% CI: 1.13, 2.22). Though the odds of early
259 neonatal mortality were greater for long birth intervals compared to the reference group, there
260 was no significant association (aOR: 1.23, 95% CI: 0.84, 1.81) (Table 2).

261 **Association of birth intervals with small birth size**

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3 262 Long birth intervals appeared to be associated with increased odds of small birth size compared
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5 263 to the reference birth interval (aOR: 1.17, 95% CI: 1.02, 1.34), while for short birth intervals,
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7 264 the odds of small birth size were smaller (aOR: 1.04, 95% CI: 0.90, 1.20) compared to the
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9 265 reference birth interval (Table 2).

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13 266 A history of pregnancy loss can be a determinant of birth interval and we therefore restricted
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15 267 our analysis to the infants whose mothers had a history of any previous pregnancy loss for all
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17 268 three outcomes. However, we found no significant relationship for either short or long birth
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19 269 intervals with all three outcomes, though for both short and long birth intervals, there was an
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21 270 increase in the odds for first-day and early neonatal death (Table 3).

26 271 **DISCUSSION**

27
28 272 This study suggests that both short and long birth intervals were associated with adverse
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30 273 pregnancy outcomes. Over the six surveys, a major proportion of infants who died on the first-
31
32 274 day, or in the first week or with a small birth size were born before the recommended optimal
33
34 275 birth interval (36–59 months). We found that a birth-to-birth interval shorter than 36 months
35
36 276 was associated with increased odds of multiple adverse pregnancy outcomes including first-
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38 277 day neonatal mortality and early neonatal mortality. Also, a birth-to-birth interval longer than
39
40 278 59 months was associated with increased odds of first-day neonatal mortality and small birth
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42 279 size.

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47 280 Infants born with a short birth-to-birth interval of less than 36 months had higher odds of first-
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49 281 day neonatal mortality. Several studies have reported an association of a short birth interval
50
51 282 with perinatal or neonatal mortality.^{19 20} However, to the best of our knowledge, no prior
52
53 283 research has examined the effect of birth interval on first-day neonatal mortality individually.
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55 284 Further, we found that the odds of early neonatal mortality were also greater among infants
56
57 285 who were born following a short birth interval. This is consistent with the findings of previous
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3 286 investigations from other LMICs which examined the effect of short birth intervals on
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5 287 perinatal, early neonatal or neonatal mortality.^{19 20} Similar to our findings, a previous study
6
7 288 conducted in India reported an association of neonatal death with a birth interval of less than
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9 289 36 months (aOR: 1.78, 95% CI: 1.63, 1.94), compared to births spaced 36–59 months.²⁰ Again,
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11 290 an analysis of 47 Demographic Health Surveys also supports our finding of higher odds of
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13 291 early neonatal mortality for short birth intervals, although this analysis has used slightly
14
15 292 different definitions of both the short birth interval (<24 months) and the reference category
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17 293 (24–<60 months).²¹ Further, our finding is in line with the finding of a previous study conducted
18
19 294 in Matlab, Bangladesh, where they reported an increased risk of very short birth intervals (less
20
21 295 than 15 months) on early neonatal mortality compared to those born after 36–59 months, though
22
23 296 in their study the risk of early neonatal mortality goes down as the birth interval increases up
24
25 297 to a minimum of 24–59 months, which is not consistent with our findings.¹² Further, we did not
26
27 298 find any significant association between short birth interval and small birth size, although
28
29 299 infants born following a short interval were at increased odds of being born with a small birth
30
31 300 size. In BDHS, birthweight is not routinely collected and birth size is based on maternal
32
33 301 perceptions of infant birth size which could lead to errors in the estimation of small birth size
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35 302 and may be responsible for this non-association. However, the direction of the effect is
36
37 303 consistent with several earlier investigations including a meta-analysis of 69 studies from both
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39 304 developing and developed countries.^{4 19 22}

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41 305 Several hypotheses have been proposed to explain the association between short birth intervals
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43 306 and adverse pregnancy outcomes.²³ One of the most frequently used hypotheses is the maternal
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45 307 nutritional depletion phenomenon, which has been defined by Winkvist et al. as a negative
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47 308 change in maternal nutritional status during a reproductive cycle, mostly due to the biological
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49 309 competition between mother and the growing fetus.^{24–26} Short birth spacing does not allow
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51 310 mothers sufficient time to restore nutritional reserves needed to support fetal growth and
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3 311 development during the subsequent pregnancy. This eventually causes maternal nutritional
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5 312 depletion that leads to the increase risk of adverse pregnancy outcomes among the births spaced
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7 313 after a short interval. Another explanation is that the association of short birth intervals and
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9 314 adverse pregnancy outcomes could be confounded by other factors including young maternal
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11 315 age, lower socio-economic status and lower utilisation of health services.^{27 28} In our analysis,
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13 316 after adjusting for maternal age, socio-economic factors, and maternal characteristics as well
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15 317 as health service related factors, a short birth interval remained associated with first-day and
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17 318 early neonatal mortality which is in line with other studies from both LMICs and high income
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19 319 countries which controlled for similar variables.^{12 15 29 30}

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24 320 Our study further identified the association of a long birth interval with adverse perinatal
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26 321 outcomes and found that infants born after a long birth interval were at greater odds of first-
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28 322 day neonatal mortality. The effect of long birth intervals on early neonatal mortality was also
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30 323 greater but was not significant. There are only a few published studies on the effect of a long
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32 324 birth interval on adverse pregnancy outcomes in LMICs and the results are conflicting.^{4 19 20} In
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34 325 contrast to our findings, a previous investigation conducted in India, examined the effect of a
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36 326 long birth interval for perinatal death and did not find any association,¹⁹ and a pooled analysis
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38 327 of 47 Demographic Health Surveys examined the effect of a longer birth interval for neonatal
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40 328 mortality and found that the odds were lower for the longer preceding birth intervals (≥ 60
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42 329 months) (OR: 0.80, 95% CI: 0.67, 0.95) compared to the birth interval of 24-<60 months.²¹
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44 330 The inconsistency in findings could be attributed to methodological differences in both the
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46 331 reference category (36-59 months vs. 24-<60 months) of the main exposure variable and the
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48 332 difference in the outcome variable (early neonatal mortality vs. neonatal mortality). However,
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50 333 our findings are consistent with a meta-analysis which reported higher odds of early neonatal
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52 334 mortality with a longer interval,⁴ and Rutstein's study which analysed data from 17 developing
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54 335 countries.⁹ Again, we found that a long birth interval was associated with greater odds of small
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3 336 birth size, similar to a few prior studies which also suggested the detrimental effect of a long
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5 337 birth interval on birth size.^{4 19 31}
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8 338 The increased odds of adverse pregnancy outcomes for long birth intervals may be due to
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10 339 concurrent factors such as advanced maternal age and previous history of pregnancy loss. In
11
12 340 an earlier investigation, Zhu et al. explained the association between long birth intervals and
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14 341 adverse pregnancy outcomes through the gradual decline in the maternal physiological and
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16 342 anatomical capacities of the reproductive system, hypothesising that if a woman does not
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18 343 conceive for an extended time after a delivery, her physiological characteristics may return to
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20 344 her unprepared primigravid state.³² Further research is needed to understand the relationship.
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25 345 **Strengths and limitations**

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27 346 The main strength of our study is that it was based on a large nationally representative sample
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29 347 from six surveys within an 18-year time period in a single country which would improve the
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31 348 homogeneity of the data. We restricted our analysis to the most recent live births within the
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33 349 five years prior to the interview date to minimise recall bias. Furthermore, we were able to add
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35 350 a number of potential confounding factors.
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40 351 We acknowledge some methodological limitations. First, this is cross-sectional data, which
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42 352 may limit the identification of a causal relationship between the birth interval and adverse
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44 353 pregnancy outcomes. Secondly, BDHS data relies on maternal recall and report of the
45
46 354 information regarding preceding birth intervals and the days of infant deaths, which are subject
47
48 355 to recall bias. Third, there is a possibility of underreporting of infant deaths, as birth histories
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50 356 and infant survival information were only collected from surviving mothers and there is a
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52 357 strong association between maternal and infant deaths. Fourth, we acknowledge a limitation of
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54 358 using maternal perception on infant birth size instead of infant birthweight in our analysis due
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56 359 to unavailability of actual estimates of birthweight in BDHS, which may reflect newborn's
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3 360 overall health status rather than birthweight only. Fifth, as we pooled six BDHS datasets over
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5 361 18 years, there may be a possibility of changes in the background characteristics of the
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7 362 population over 18 years. Furthermore, in our analysis, we were unable to include the variable
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9 363 regarding the history of immediate previous adverse outcome such as stillbirth, miscarriage
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11 364 etc. which is a determinant of adverse perinatal outcomes in a subsequent pregnancy. A
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13 365 previous investigation conducted in Bangladesh using dynamic panel data models, reported
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15 366 that a previous adverse birth outcome may be subject to a ‘scarring effect’ which leads to a
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17 367 short birth interval (replacement) and thus increases the risk of mortality of the subsequent
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19 368 infant (nutritional depletion); as a mother with a previous pregnancy loss may rush into a
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21 369 pregnancy without properly recovering from the pregnancy loss.³³ In our analysis, we were
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23 370 unable to consider the role of ‘scarring effect’ related to a previous adverse pregnancy outcome
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25 371 which has an influence on birth interval. To account for this, we were able to stratify our
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27 372 analysis by the variable ‘ever had a pregnancy loss’, although that stratification increased the
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29 373 effect sizes of first-day and early neonatal mortality for both short and long birth intervals,
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31 374 neither were significant.
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38 375 **CONCLUSIONS**

39
40 376 Our analysis supports the reduced risk of adverse pregnancy outcomes following a birth-to-
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42 377 birth interval of 36-59 months which is consistent with the WHO recommendation of a birth-
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44 378 to-pregnancy interval of 24 months. Our results highlight several important implications for
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46 379 care-providers, program managers and policymakers by suggesting that a preceding birth
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48 380 interval of 36-59 months could prevent adverse pregnancy outcomes including first-day
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50 381 neonatal death, early neonatal death and low birthweight. Promoting an optimal birth interval
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52 382 of 36-59 months through postpartum family planning may reduce perinatal and neonatal
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54 383 mortality.
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4

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10
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12
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18 390 **Authors' contributions**
19

20 391 MKN, CRG and AA conceptualised and designed the study. MKN performed the literature
21
22 392 review. MKN, CRG, MTI and TH performed statistical analysis. MKN and CRG drafted the
23
24 393 manuscript. MKN and CRG contributed to the interpretation of the data. MKN, CRG, AA and
25
26 394 MTI contributed to the critical revision of the manuscript. All the authors read and approved
27
28 395 the final manuscript.
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32

33 396 **Conflict of interest**
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35 397 We declare that we have no conflict of interest.
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37

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39

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41
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45 401 **Data sharing statement**
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47 402 The data are anonymous and publicly available in the website; www.measuredhs.com.
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Table 1: First-day neonatal mortality, early neonatal mortality and small birth size infants by maternal characteristics in Bangladesh: BDHS 1996-2014

Predictors	First-day neonatal mortality (N= 21,382) n (%) n=115	Early neonatal mortality (N= 21,382) n (%) n=274	Small birth size (N= 11,022) n (%) n=2,002
Preceding birth interval in months			
<36 months	49 (45.2)	122 (45.2)	698 (34.6)
36-59 months	22 (18.8)	70 (26.2)	610 (31.2)
≥ 60 months	44 (36.0)	82 (28.6)	694 (34.2)
Mother's age at childbirth			
≤19 years	20 (21.1)	40 (16.2)	218 (10.7)
20-34 years	82 (67.5)	200 (71.5)	1599 (80.0)
≥35 years	13 (11.4)	34 (12.3)	185 (9.3)
Birth order			
2-3	73 (63.3)	163 (60.0)	1322 (65.8)
≥4	42 (36.7)	111 (40.0)	680 (34.2)
Maternal education			
None	40 (36.4)	116 (42.0)	751 (38.3)
Primary	41 (33.7)	84 (30.6)	618 (29.0)
Secondary or higher	34 (29.9)	74 (27.4)	633 (32.7)
Wealth index			
Poorest quintile	24 (19.6)	71 (23.5)	428 (19.6)
Second quintile	24 (21.6)	63 (24.0)	394 (19.8)
Middle quintile	24 (19.5)	57 (22.2)	389 (19.4)
Fourth quintile	20 (20.2)	35 (13.5)	388 (20.7)
Richest quintile	23 (19.1)	48 (16.8)	403 (20.5)
Employment status			
Currently working	34 (32.1)	70 (28.0)	339 (18.0)
Not working	81 (67.9)	204 (72.0)	1663 (82.0)
Area of residence			
Urban	35 (20.8)	81 (19.0)	557 (20.1)
Rural	80 (79.2)	193 (81.0)	1445 (79.9)
Maternal BMI			
Underweight	27 (23.1)	83 (29.3)	711 (35.3)
Average	67 (59.2)	156 (58.4)	1069 (54.5)
Overweight	16 (13.1)	26 (9.3)	169 (7.9)
Obese	5 (4.6)	9 (3.0)	53 (2.3)

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4	Maternal desire of			
5	pregnancy			
6	Yes	77 (63.3)	171 (63.5)	1205 (60.1)
7	No	38 (36.7)	103 (36.5)	797 (39.9)
8				
9	Ever use of contraception			
10	Yes	81 (72.9)	196 (71.9)	1605 (81.1)
11	No	34 (27.1)	78 (28.1)	397 (18.9)
12				
13	No. of ANC visits			
14	None	48 (43.1)	146 (55.2)	998 (51.4)
15	1-3 visits	46 (40.7)	90 (32.0)	683 (33.7)
16	≥4 visits	21 (16.2)	38 (12.8)	321 (14.9)
17				
18				
19	ANC by SBA			
20	Yes	56 (47.3)	111 (38.6)	817 (38.8)
21	No	59 (52.7)	163 (61.4)	1185 (61.2)
22				
23				
24	History of any previous			
25	pregnancy loss			
26	Yes	35 (26.3)	79 (26.2)	435 (21.4)
27	No	80 (73.7)	195 (73.8)	1567 (78.6)
28				
29				
30	Sex of infant			
31	Male	74 (64.1)	162 (58.0)	943 (44.9)
32	Female	41 (35.9)	112 (42.0)	1059 (55.1)
33				
34	Region			
35	Barisal	10 (4.2)	28 (5.5)	176 (4.7)
36	Chittagong	12 (10.1)	40 (13.9)	463 (25.4)
37	Khulna	10 (8.2)	27 (9.0)	232 (8.6)
38	Rajshahi	27 (25.1)	50 (20.9)	227 (13.2)
39	Rangpur	15 (8.0)	47 (10.7)	235 (8.2)
40	Sylhet	10 (3.5)	18 (3.5)	281 (7.1)
41	Dhaka	31 (40.9)	64 (36.5)	388 (32.8)
42				
43				
44				
45	Year of survey			
46	1996	16 (14.0)	45 (15.8)	-
47	1999	13 (10.7)	45 (15.8)	705 (34.2)
48	2004	22 (20.1)	55 (21.2)	-
49	2007	19 (17.9)	37 (13.6)	-
50	2011	29 (24.1)	59 (21.5)	813 (40.1)
51	2014	16 (13.2)	33 (12.1)	484 (25.7)
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Table 2: Results of multivariable analysis for the association between preceding birth intervals and adverse pregnancy outcomes in Bangladesh:

BDHS 1996-2014

Predictors	First-day neonatal mortality N=21,382		Early neonatal mortality N=21,382		Small birth size N=11,022	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Preceding birth interval in months						
<36 months	2.11 (1.17, 3.78)	<0.05	1.58 (1.13, 2.22)	<0.05	1.04 (0.90, 1.20)	0.08
36-59 months	Reference		Reference		Reference	
≥60 months	2.02 (1.10, 3.73)		1.23 (0.84, 1.81)		1.17 (1.02, 1.34)	
Mother's age at childbirth						
≤19 years	2.51 (1.35, 4.66)	<0.05	1.53 (1.02, 2.28)	<0.05	1.01 (0.83, 1.21)	0.68
20-34 years	Reference		Reference		Reference	
≥35 years	1.34 (0.67, 2.69)		1.46 (0.93, 2.29)		1.10 (0.89, 1.36)	
Birth order						
2-3	Reference		Reference		Reference	
≥4	1.48 (0.88, 2.50)	0.14	1.27 (0.92, 1.75)	0.15	1.02 (0.89, 1.16)	0.81
Maternal education						
None	0.97 (0.49, 1.94)	0.80	0.94 (0.60, 1.46)	0.94	1.09 (0.91, 1.30)	0.05
Primary	1.15 (0.62, 2.11)		0.98 (0.65, 1.50)		0.91 (0.77, 1.07)	
Secondary or higher	Reference		Reference		Reference	
Wealth status						
Poorest quintile	0.76 (0.34, 1.68)	0.89	0.86 (0.53, 1.40)	0.68	1.30 (1.05, 1.61)	<0.05
Second quintile	0.92 (0.43, 1.95)		0.99 (0.61, 1.63)		1.34 (1.09, 1.64)	
Middle quintile	0.97 (0.48, 1.96)		1.09 (0.70, 1.72)		1.12 (0.91, 1.37)	
Fourth quintile	1.15 (0.58, 2.28)		0.80 (0.48, 1.32)		1.12 (0.93, 1.37)	

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2							
3	Richest quintile	Reference		Reference		Reference	
4							
5	Employment status						
6	Currently working	1.59 (0.99, 2.56)	0.05	1.30 (0.96, 1.75)	0.09	1.02 (0.87, 1.19)	0.83
7	Not working	Reference		Reference		Reference	
8							
9							
10	Area of residence						
11	Urban	1.10 (0.64, 1.88)	0.72	1.14 (0.80, 1.63)	0.46	1.09 (0.93, 1.27)	0.28
12	Rural	Reference		Reference		Reference	
13							
14							
15	Maternal BMI						
16	Underweight	0.58 (0.35, 0.97)	<0.05	0.70 (0.52, 0.94)	0.05	1.19 (1.05, 1.34)	<0.05
17	Average	Reference		Reference		Reference	
18	Overweight	1.81 (0.90, 3.65)		1.36 (0.80, 2.32)		0.86 (0.70, 1.07)	
19	Obese	1.84 (0.59, 5.67)		1.23 (0.53, 2.89)		0.86 (0.60, 1.23)	
20							
21							
22	Maternal desire of pregnancy						
23	Yes	1.09 (0.71, 1.68)	0.68	1.13 (0.84, 1.51)	0.43	0.92 (0.81, 1.05)	0.22
24	No	Reference		Reference		Reference	
25							
26							
27	Ever use of contraception						
28	Yes	Reference		Reference		Reference	
29	No	2.20 (1.32, 3.68)	<0.05	1.89 (1.35, 2.64)	<0.001	1.23 (1.06, 1.42)	<0.05
30							
31							
32	No of ANC visits						
33	None	0.89 (0.29, 2.73)	0.62	1.61 (0.74, 3.48)	0.48	1.09 (0.84, 1.42)	0.79
34	1-3 visits	1.21 (0.61, 2.37)		1.16 (0.71, 1.89)		1.03 (0.86, 1.23)	
35	≥4 visits	Reference		Reference		Reference	
36							
37							
38	ANC by SBA						
39	Yes	Reference		Reference		Reference	
40							
41							
42							
43							
44							
45							
46							

No	1.01 (0.46, 2.19)	0.99	0.78 (0.43, 1.42)	0.42	1.05 (0.83, 1.32)	0.70
History of any previous pregnancy loss						
Yes	1.31 (0.85, 2.03)	0.22	1.27 (0.94, 1.71)	0.12	1.04 (0.91, 1.20)	0.53
No	Reference		Reference		Reference	
Sex of infant						
Male	1.70 (1.09, 2.64)	<0.05	1.32 (1.01, 1.73)	<0.05	0.71 (0.63, 0.80)	<0.001
Female	Reference		Reference		Reference	
Region						
Barisal	0.59 (0.27, 1.30)	<0.05	0.82 (0.51, 1.30)	<0.05	0.74 (0.59, 0.92)	<0.001
Chittagong	0.34 (0.16, 0.71)		0.50 (0.32, 0.77)		1.16 (0.97, 1.38)	
Khulna	0.72 (0.35, 1.50)		0.91 (0.57, 1.44)		0.96 (0.79, 1.17)	
Rajshahi	1.12 (0.63, 1.99)		1.02 (0.68, 1.53)		0.73 (0.60, 0.89)	
Rangpur	0.68 (0.35, 1.29)		0.99 (0.66, 1.51)		0.81 (0.65, 0.99)	
Sylhet	0.83 (0.36, 1.88)		0.92 (0.53, 1.61)		1.24 (1.03, 1.50)	
Dhaka	Reference		Reference		Reference	

*Odds ratios were adjusted for maternal age at childbirth, birth order, maternal education, maternal wealth index, maternal employment status, area of residence, maternal BMI, maternal desire of pregnancy, ever use of contraceptive method, number of ANC visits, ANC by SBA, history of any previous pregnancy loss, sex of infant and region

Table 3: Results of multivariable analysis for the association between preceding birth intervals and adverse pregnancy outcomes by history of any previous pregnancy loss: BDHS 1996-2014

Predictors	First-day neonatal mortality N=21,382		Early neonatal mortality N=21,382		Small birth size N=11,022	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Preceding birth interval in months*history of any previous pregnancy loss						
<36 months	2.12 (0.74, 6.13)	0.28	1.77 (0.90, 3.49)	0.19	0.96 (0.69, 1.33)	0.38
36-59 months	Reference		Reference		Reference	
≥60 months	2.15 (0.73, 6.31)		1.74 (0.84, 3.62)		1.18 (0.87, 1.59)	

*Odds ratios were adjusted for maternal age at childbirth, birth order, maternal education, maternal wealth index, maternal employment status, area of residence, maternal BMI, maternal desire of pregnancy, ever use of contraceptive method, number of ANC visits, ANC by SBA, sex of infant and region

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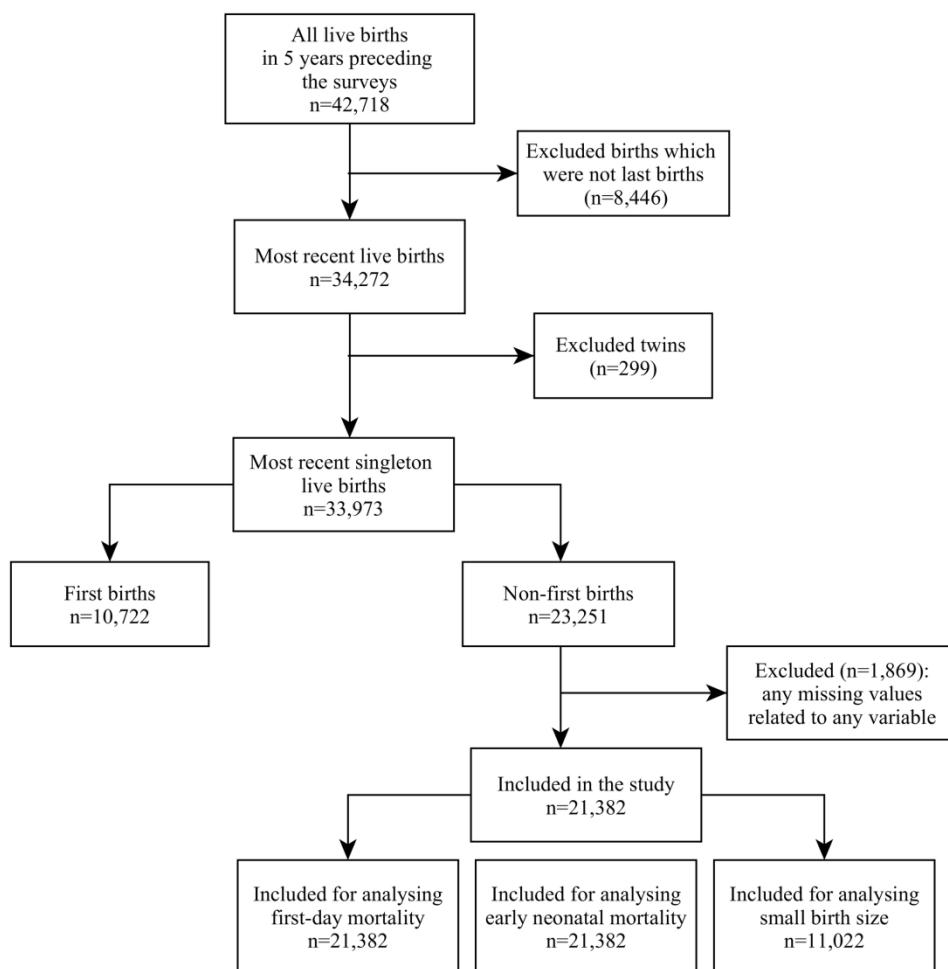


Figure 1: Flow diagram showing sample selection for first-day neonatal mortality, early neonatal mortality and small birth size analysis

203x205mm (300 x 300 DPI)

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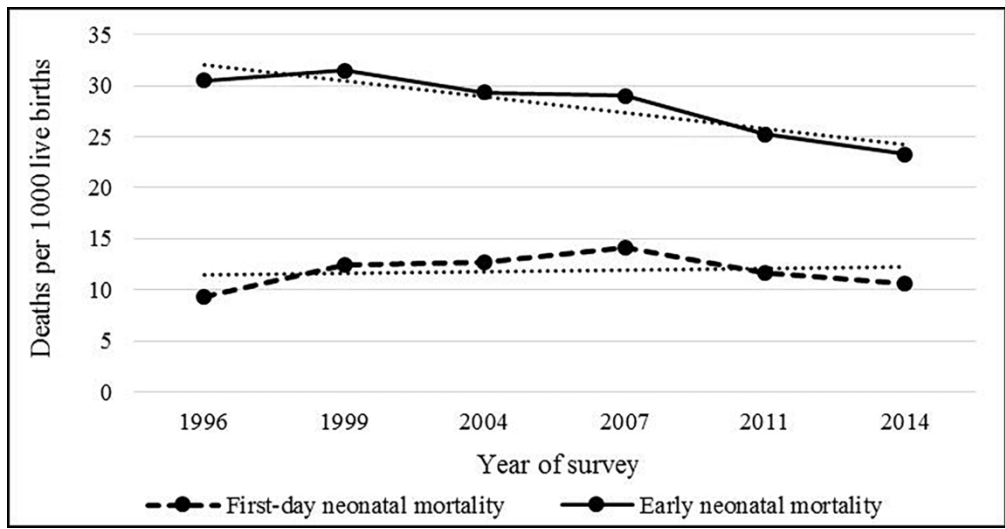


Figure 2: Trends in first-day and early neonatal mortality by year of survey (1996-2014)

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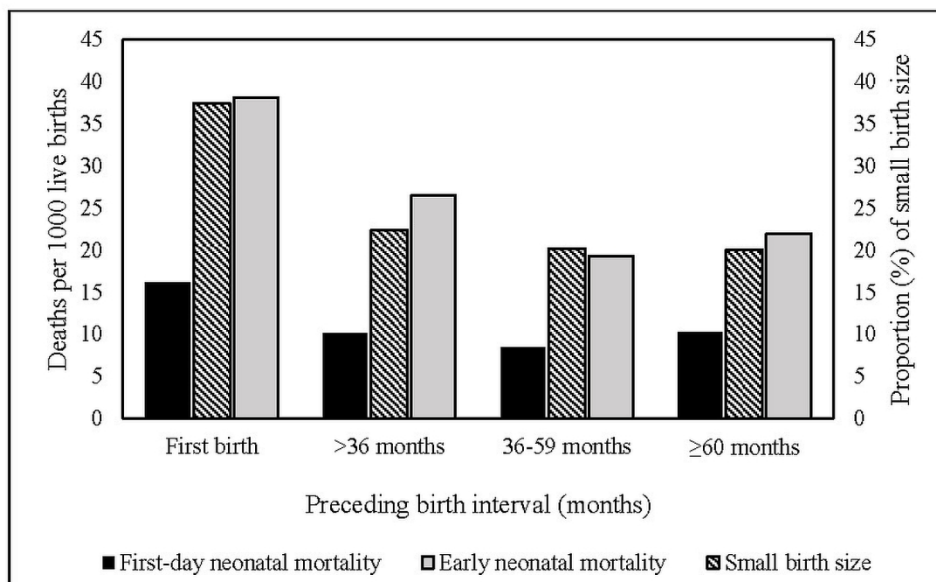


Figure 3: First-day neonatal mortality, early neonatal mortality rates per 1000 live births and the proportion of small birth size by preceding birth intervals

149x101mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*:
 Manuscript ID bmjopen-2018-024392

	Item No	Recommendation	Reported on page no.
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 2, line 31
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2, line 30-38, 41-49
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5, line 71-99
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5, line 99-104
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5-6, line 107-124
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5-6, line 107-124
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Page 6, line 122-124
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7, line 125-160
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	Page 6, line 125-135
Bias	9	Describe any efforts to address potential sources of bias	Page 6, line 122-124
Study size	10	Explain how the study size was arrived at	Page 5-6, line 107-124, Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7-8, line 162-186
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 7-8, line 162-187
		(b) Describe any methods used to examine subgroups and interactions	Page 8, line 181-183
		(c) Explain how missing data were addressed	Figure 1
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	Page 8, line 181-183
Results			
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	Figure 1, Page 9, line 197-215

		follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Page 9, line 206-212
		(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	Table 1, Page 10-11, line 219-243
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures	Table 1
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	Table 2
		(b) Report category boundaries when continuous variables were categorized	Page 7, line 144-146, 150
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12, line 269-276
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	Page 15, line 348-371
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12-15, line 269-341
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 16, line 373-379
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	N/A