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A M E R I C A N C O L L E G E O F



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Asthma prevalence, family size and birth order

Shmuel Goldberg¹, MD; Eran Israeli^{2,3}, MD; Shepard Schwartz⁴, MD; Tzippora Shochat³, M.Sc; Gabriel Izbicki⁵, MD; Ori Toker-Maimon⁴, MD; Eyal Klement, DVM³ and Elie Picard¹, MD.

From the Departments of Pediatric Pulmonology (1), Pediatrics (4), Institute of Pulmonology (5), Shaare Zedek Medical Center, Jerusalem, Israel; Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheva, Israel, and from Department of Medicine, Hebrew University- Hadassah Medical Center, Jerusalem, Israel (2) and IDF Medical Corps (3).

The work was performed in Shaare Zedek Medical Center. S. Goldberg and E. Israeli contributed equally to the study.

Corresponding Author:

Shmuel Goldberg M.D.,
Pediatric Pulmonology
Shaare Zedek Medical Center
P.O.B. 3235
Jerusalem 91301, Israel.
Tel: 972-2-6666292, Fax: 972-2-6555226
Email: sgoldberg@szmc.org.il

Authors e-mail addresses:

Eran Israeli: eran-i@bezeqint.net; Shepard Schwartz: sls909@yahoo.com; Tzippora Shochat: raz-shai@bezeqint.net; Gabriel Izbicki: Izbicki@szmc.org.il; Ori Toker-Maimon: oritokerm@szmc.org.il; Eyal Klement: klement@agri.huji.ac.il; Elie Picard: picard@szmc.org.il

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1 **Key words**

2

3 Asthma, Epidemiology, Pediatrics

4

5

1 **Abstract**

2 **Background**

3 Asthma prevalence may be reduced in large families. The hygiene hypothesis
4 suggests that older siblings protect their younger siblings from asthma through a
5 modulating effect on the yet maturing immune system. If the hygiene hypothesis is
6 correct, asthma prevalence should be inversely related to birth order.

7 The objective of this study was to examine the relationship between asthma
8 prevalence, family size and birth order.

9

10 **Methods**

11 The medical records of 531,116 Israeli conscripts were reviewed. Association
12 between number of children in the family and prevalence of asthma, and between
13 birth order and prevalence of asthma was assessed. Odds ratios for asthma by birth
14 order and family size, adjusted for each other, were calculated.

15

16 **Results**

17 Asthma was diagnosed in 26,833 males (8.6%) and in 15,079 females (6.9%). Asthma
18 prevalence was inversely related to the number of children in the family ($p < 0.001$).

19 Among subjects who were the only child in the family, prevalence of asthma was
20 7.3%. The prevalence increased to 8.95% among subjects from families with three
21 siblings, and then progressively decreased as the number of siblings increased, and
22 reached a trough of 0.58% in conscripts from families of 15-20 siblings. Asthma
23 prevalence was similar for all birth orders.

24

25

1 **Conclusions**

2 In families with 4 or more children, asthma prevalence is inversely related to the
3 number of children in the family. Asthma prevalence is similar for all birth orders.
4 The similar asthma prevalence for all birth orders challenges the hygiene hypothesis
5 as the mechanism for the decreased asthma prevalence in large families.

6

7

1 **Introduction**

2 The existence of an association between size of families and prevalence of asthma has
3 been the subject of considerable study, and thus far remains a matter of controversy.
4 Several studies found a negative association between asthma prevalence and family
5 size (1-4). By contrast one study detected a higher asthma prevalence in larger
6 families (5), while some researchers found no association at all between the two (2,6).

7

8 If multiple siblings do offer a protective effect against asthma, it is unclear if this
9 applies to all children, or only to those of higher birth order. Studies that demonstrated
10 an inverse relation between birth order and asthma risk (7,8), did not correct this
11 finding for family size. Hence, it is possible that what was presented as the protective
12 effect of high birth order, may actually be that of large family size.

13

14 Theories which explain the mechanism of the sibling's protective effect, have
15 potentially broad implications, as they may shed light on asthma pathogenesis. The
16 leading theory, the "hygiene hypothesis" (9), is predicated on the assertion that
17 exposure to bacterial components protects from asthma through an effect on the
18 relatively immature immune system of early childhood, thereby preventing a
19 proclivity towards atopy. The theory suggests that the presence of older siblings
20 increases the child's exposure to bacterial burden (9). Accordingly, a higher degree of
21 protection is anticipated among the younger siblings, since they are exposed to more
22 children at home during early childhood.

23

24 The aim of this study was to examine the relationship between asthma and both
25 family size and birth order. We specifically wished to assess the effect of birth order

1 on asthma prevalence for each particular family size, including relatively large
2 families. A large population pool with a high number of subjects belonging to families
3 of four or more children was therefore chosen for study. This enabled the subdivision
4 of the study population into large groups of subjects from each particular family size,
5 and thus the separate evaluation of the effect of birth order for each family size.

6

7

1 **Methods**

2 The medical records of all 17 year old Israeli conscripts who underwent compulsory
3 medical evaluation between 1998-2004 were reviewed. In this age group, the vast
4 majority of the population in Israel (excluding Israelis of Arab origin and Jewish
5 orthodox females) undergoes a comprehensive medical evaluation in military
6 recruitment offices prior to obligatory military service. As of the end of year 2004,
7 close to 7,000,000 people resided in Israel, with 92% of them dwelling in urban areas
8 (10).

9

10 Performed by a trained physician, the evaluation entails a detailed medical history that
11 includes both a personal interview and review of a preformed questionnaire completed
12 by the family physician. A complete physical examination is performed. Based on the
13 above information, the examining physician may assign a particular medical diagnosis
14 to the conscript. All diagnoses are coded and stored in a computerized database.

15 Army physicians are instructed to assess each conscript for asthma based on the
16 medical summary of the family physician, the medical history, physical examination
17 and documented use of asthma therapy. Conscripts who previously had asthma but no
18 longer had symptoms at the time of the exam, were still diagnosed with asthma.

19 Spirometry, exercise challenge test and methacoline challenge test, are performed
20 (according to the American Thoracic Society guidelines (11)) in cases of doubt. Upon
21 completion of the evaluation process, if asthma is diagnosed, the diagnosis is entered
22 into the database.

23

24 Information retrieved from the military database for our evaluation included presence
25 or absence of the diagnosis of asthma, gender, the number of children in the family,

1 birth order and country of origin. Country of origin was categorized according to the
2 paternal birthplace as follows: Israel, Western countries (Europe and America), Asia,
3 former USSR, Africa excluding Ethiopia, and Ethiopia. Information concerning atopic
4 phenomena is not collected systematically and therefore was not included in the
5 analysis.

6

7 The protocol was reviewed and approved by the Human Use Committee of the IDF-
8 Medical Corps. In order to protect the privacy of the subjects, the army did not release
9 their names nor any sensitive personal information.

10

11 Statistical calculations were performed using the SAS (version 9.2) software.
12 Significance of association between number of children in the family and prevalence
13 of asthma, and between birth order and prevalence of asthma was assessed by Mantel-
14 Haenzel statistics for trends. Odds ratio (OR) for asthma by number of children in
15 family was calculated, adjusted for birth order and country of origin. Odds ratio for
16 asthma by birth order was similarly calculated, adjusted for the number of children in
17 the family and country of origin.

18

19

20

1 **Results**

2 Data regarding 531,116 conscripts were evaluated. Of these, 312,888 were male
3 (58.9%) and 218,228 (41.1%) female. Asthma was diagnosed in 26,833 males (8.6%)
4 and was less frequent in females (15,079, (6.9%)). Asthma prevalence according to
5 paternal country of origin is presented in Table 1.

6
7 Asthma prevalence was inversely related to the number of children in the family
8 (Graph 1). Among subjects who were the only child in the family, prevalence of
9 asthma was 7.3%. The prevalence increased to 8.95% among subjects from families
10 with three siblings, and then progressively decreased as the number of siblings
11 increased, reaching a trough of 0.58% in conscripts from families of 15-20 children.
12 Hence, the prevalence of asthma in conscripts from families with 3 children is
13 approximately 15 times higher than that from families with 15-20 children. The
14 association between the number of children in the family and prevalence of asthma is
15 significant ($p < 0.001$, Mantel-Haenzel statistics for trends).

16
17 Although asthma prevalence was lower in larger families, it was similar for all birth
18 orders. For each individual family size group, there was no association between birth
19 order and prevalence of asthma ($P > 0.05$, Table 2).

20
21 Odds Ratios for asthma according to the number of children in the family adjusted for
22 birth order and country of origin are presented in Table 3. There is a constant inverse
23 relationship between OR for asthma and family size. In subjects from families with
24 10-14 children, the OR for asthma is approximately one fifth of that in single child
25 families. Of note, in comparison to males from families with one child, the OR for

1 asthma among males from families with 2 or 3 children first increases, and
2 subsequently decreases among males from families with 4 or more children. Among
3 females, there is a consistent decrease in the OR with each increment in family size.
4 In contrast, the odds ratio for asthma by birth order adjusted for number of children,
5 demonstrated no association between birth order and asthma prevalence (Table 4).

6

7

1 **Discussion**

2 In this large retrospective study of the majority of the 17-year-old Israeli population
3 during a 7 year period, we found that in families of 4 or more children, asthma
4 prevalence is inversely related to family size.

5 As noted earlier, the possibility of an association between family size and prevalence
6 of asthma is a matter of controversy. In their review of the literature Karmaus and
7 Botezan (2) found 18 studies showing a statistically significant inverse relationship
8 between family size and prevalence of asthma, and 7 studies which demonstrated no
9 relationship. Our study, due to the exceptionally high number of subjects, many of
10 them from families of 4 children or more, offers strong support that asthma
11 prevalence is lower in larger families. To the best of our knowledge, it is the largest
12 study evaluating the correlation between both number of children and birth order with
13 the prevalence of asthma.

14 A negative correlation between prevalence of allergic disease and family size was first
15 observed by Golding and Peters (12). Strachan suggested the "hygiene hypothesis" as
16 the explanation for this phenomenon, according to which "allergic diseases are
17 prevented by infection in early childhood, transmitted by unhygienic contact with
18 older siblings, or acquired prenatally from a mother infected by contact with her older
19 children" (9). This hypothesis has been expanded to explain the inverse relationship
20 between asthma prevalence and family size as well (2). In addition to infections, other
21 forms of bacterial burden including microbial components such as endotoxin,
22 gastrointestinal colonization and soil microbiota are also thought to influence allergy
23 and asthma outcomes (13). The immunological mechanisms underlying the protection
24 against allergies mediated by living in a less hygienic environment is under debate,

1 and might include skewing of the T_H1/T_H2 balance away from allergy-promoting T_H2
2 cells toward T_H1 cells, influence on T regulatory cells or modulation of the innate
3 immune system (14).

4 Interestingly, we did not find an association between birth order and asthma
5 prevalence. Studies that evaluated the association between asthma prevalence and
6 birth order adjusted for family size are scant. Jarvis et al (15) examined a small
7 sample of 1159 adult asthma patients between the ages of 20-44 years, and obtained
8 results similar to ours. In their study, asthma prevalence correlated inversely with
9 family size, and was unassociated with birth order. In contrast, Bernsen et al (16)
10 assessed 700 families and found asthma prevalence to be unrelated to both family size
11 and birth order. The small sample size may account for these findings.

12

13 The finding that asthma prevalence is similar for all birth orders challenges the
14 hygiene hypothesis as an explanation for the decreased asthma prevalence in larger
15 families. Since, according to the hygiene hypothesis, the time in which the immune
16 system matures either normally or toward atopy is early childhood (6,9,17-22), and
17 since older children were exposed to fewer siblings during their early childhood, we
18 would expect older siblings to have a higher prevalence of asthma than their younger
19 siblings.

20

21 The “prenatal programming” theory was suggested as an alternative to the “hygiene
22 hypothesis” (2,23,24). It posits that the lower prevalence of asthma among children
23 from large families stems from a maternal protective effect on her high birth order
24 offspring. The inverse relationship between cord IgE levels and the number of
25 pregnancies was suggested to support to this theory (23). The lack of correlation

1 between asthma prevalence and birth order casts doubt on the validity of the “prenatal
2 programming” theory as well. If, as this theory suggests (2,23-28), multiple
3 pregnancies provide a protective effect to the offspring, children of high birth order
4 should have a lower prevalence of asthma.

5
6 Due do the limited medical information contained within the military database we
7 could not obtain data concerning potential confounding factors that could influence
8 asthma prevalence, such as socioeconomic status, BMI, atopy, smoking history,
9 distribution of residence, and atopy in the family. It is possible then, that family size
10 in not an independent risk factor for asthma, and that the relation between asthma
11 prevalence and family size actually reflects the varied distribution of at least some of
12 these factors among families of different size. In addition, it is possible that asthma
13 among children from larger families is not less prevalent, but rather less commonly
14 diagnosed. Since parental attention to children’s medical conditions is impaired in
15 large families (29), children with asthma symptoms might not always be brought to a
16 physician for evaluation and treatment. With no suggestive history, the likelihood that
17 the examining physician will miss the diagnosis of asthma increases. The decreased
18 reproductive potential of women with atopic disease (30,31) may also contribute to
19 the higher prevalence of asthma among children from small families. In addition, the
20 higher prevalence of asthma in small families could be due to increased use of oral
21 contraceptives. Oral contraceptives are known to increase IgE levels in non-asthmatic
22 women (32), and to increase asthma risk in offspring (33).

23

24 In the current study, only 41% of the examinees were female. This is likely due to the
25 exemption of Jewish orthodox females from army service. The exclusion of a

1 significant sector from the female group, renders the socioeconomic profile of the
2 females different from that of the males. This difference may account for the lower
3 asthma prevalence among females, as well as the observation that in females, asthma
4 prevalence is inversely related to family size for every family size, while in men the
5 OR for asthma among families with 2 or 3 children first increases, and subsequently
6 decreases among families with 4 or more children. Alternatively, and possibly more
7 likely, there may exist a fundamental difference in asthma pathogenesis between the
8 two genders. Such a possibility is suggested by other differences in asthma
9 epidemiology between the genders, for example, an association between increased
10 BMI and asthma was reported in females and not in males (34).

11 In summary, in this large study we found that in families with 4 or more siblings, the
12 number of siblings in a family is inversely associated with asthma prevalence, and
13 that there is no association between asthma prevalence and birth order. The similar
14 asthma prevalence for all birth orders challenges the hygiene hypothesis as an
15 explanation for the decreased asthma prevalence in larger families.

16

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13

1 **Figure Legend**

2 **Graph 1**: Prevalence of asthma according to number of children in the family. The
3 association between number of children in the family and prevalence of asthma is
4 significant ($p < 0.001$).
5

Paternal country of origin	Number of conscripts	% With asthma
Israel	41,313	6.56
Western counties	138,247	9.2
Russia	119,46	6.38
Asia	108,311	9.28
Africa (excluding Ethiopia)	111,990	7.53
Ethiopia	11,909	4.27
Total	531,116	7.89

Table 1: Number of conscripts and asthma prevalence according to paternal country of origin.

1

Birth order	Number of children in family										
	1	2	3	4	5	6	7	8	9	10-14	15-20
All	7.31 30,435	8.71 125,464	8.95 182,678	7.47 107,200	6.34 40,679	5.35 18,236	4.26 9,724	3.13 6,259	2.81 3,808	2.06 6,106	0.58 520
1	7.31 30,435	8.76 61,657	8.92 59,899	7.44 25,740	6.46 7,601	5.78 2,854	5.66 1,273	3.37 713	3.78 370	2.22 451	0.00 19
2		8.67 63,807	8.9 62,154	7.59 27,447	6.36 8,348	5.20 3,113	4.18 1,437	3.62 829	3.93 407	3.21 529	0.00 16
3			9.02 60,625	7.45 28,386	6.38 8,953	5.00 3,318	3.68 1,605	3.25 922	1.83 492	1.52 656	0.00 38
4				7.4 25,627	6.54 7,900	5.3 2,943	3.60 1,583	2.40 918	0.61 495	1.51 661	0.00 37
5					5.95 7,877	5.43 2,892	3.73 1,126	2.61 766	2.70 519	0.98 715	0.00 45
6						5.46 3,116	4.09 1,222	1.70 528	1.94 360	1.51 595	0.00 53
7							5.01 1,478	2.60 691	4.22 332	2.07 531	0.00 49
8								4.82 892	3.41 323	2.63 419	0.00 52
9									3.73 510	2.18 413	2.7 37
10-14										2.82 1,136	0.89 112
15-20											1.61 62

2

3 **Table 2: Asthma prevalence according to birth order and number of children in**4 **family.** The first line in each box contains the percentage of conscripts with asthma.

5 The second line indicates the total number of conscripts evaluated. Data concerning 7

6 conscripts are missing. Asthma prevalence is inversely related to the number of

7 children in the family and is unrelated to birth order.

8

1

Number of children in family	Adjusted Odds Ratio (confidence limit) Male	Adjusted Odds Ratio (confidence limit) Female
1	1	1
2	1.184 (1.112-1.262)	0.962 (0.889-1.042)
3	1.073 (1.006-1.146)	0.830 (0.765-0.901)
4	0.841 (0.784-0.903)	0.715 (0.654-0.782)
5	0.686 (0.631-0.745)	0.687 (0.615-0.767)
6	0.591 (0.532-0.656)	0.604 (0.514-0.709)
7	0.463 (0.403-0.532)	0.500 (0.391-0.638)
8	0.301 (0.249-0.365)	0.456 (0.321-0.646)
9	0.281 (0.221-0.358)	0.334 (0.195-0.571)
10-14	0.183 (0.144-0.232)	0.234 (0.115-0.474)
15-20	0.038 (0.009-0.154)	<0.001(<0.001->999.999)

2

3 **Table 3:** Adjusted Odds Ratio for asthma (compared to single child family) by4 number of children in family corrected for birth order and country of origin.

5

1

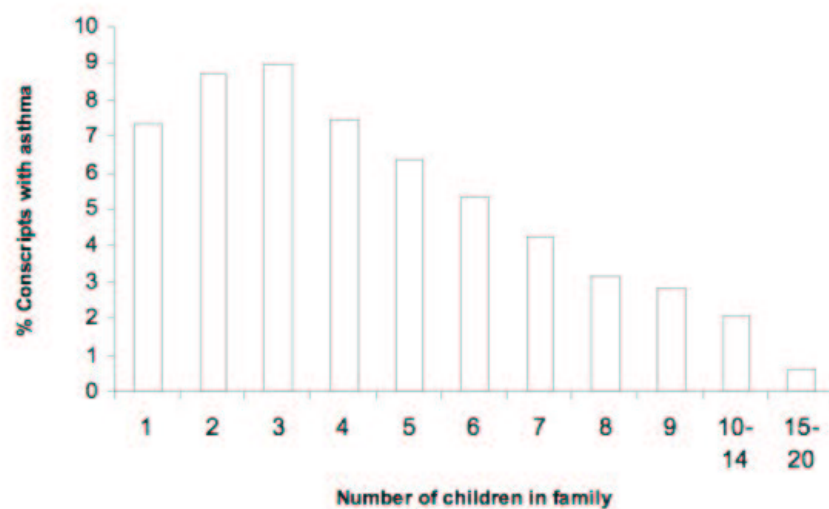
Birth Order	Adjusted Odds Ratio (confidence limit) Male	Adjusted Odds Ratio (confidence limit) Female
1	1	1
2	0.986 (0.956-1.017)	1.022 (0.981-1.065)
3	0.981 (0.945-1.019)	1.010 (0.961-1.062)
4	0.971 (0.915-1.031)	0.955 (0.881-1.036)
5	0.941 (0.848-1.044)	0.840 (0.720-0.980)
6	0.911 (0.770-1.079)	0.949 (0.728-1.235)
7	1.090 (0.856-1.386)	1.250 (0.841-1.859)
8	1.526 (1.106-2.107)	1.489 (0.852-2.602)
9	1.430 (0.910-2.248)	1.382 (0.543-3.517)
10-14	1.570 (0.999-2.465)	2.107 (0.752-5.907)
15-20	4.890 (0.434-55.065)	1.708 (<0.001->999.999)

2

3 **Table 4:** Adjusted Odds Ratio for asthma (compared to first child) by birth order

4 corrected for number of children in family and country of origin.

% Conscripts with asthma according to number of children in family



Asthma prevalence, family size and birth order

Shmuel Goldberg, Eran Israeli, Shepard Schwartz, Tzipora Shochat, Gabriel Izbicki, Ori Toker-Maimon, Eyal Klement and Elie Picard

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