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A descriptive study of asthma in young adults conceived by IVF


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Mr Nicholas Sicignano received his Master of Public Health degree, epidemiology track, from the graduate programme in public health at Eastern Virginia Medical School in 2009. He completed a Bachelor of Science degree in the area of health sciences with a Minor in public health from James Madison University in 2003. This manuscript is based on his practicum work in collaboration with the Jones Institute for Reproductive Medicine. Upon graduating, Mr Sicignano was hired as a researcher by Battelle Memorial Institute and has been contracted to work as a clinical epidemiologist at the Navy and Marine Corps Public Health Centre in Portsmouth, Virginia. Author contributions: NS participated in questionnaire design, data management, data analysis and drafted the manuscript. HAB conceived the study, performed data analysis and manuscript write-up. SO, HJ and HR were involved in study design and approval, provided data access and revised the paper for intellectual content.

Abstract Although asthma has been previously associated with preterm delivery and low birthweight, evidence supporting a relationship between IVF and asthma remains inconclusive. The purpose of this study was to characterize asthma experiences in the oldest IVF-conceived generation in the USA. A cross-sectional study was conducted among 173 young adults (age: 18–26 years) conceived by conventional IVF between 1981 and 1990 at a major fertility treatment centre. A self-administered questionnaire was used with standard questions adapted from the 2008 Behavioural Risk Factor Surveillance System to assess asthma characteristics. Sixteen percent of participants reported a lifetime diagnosis of asthma; nearly half of those were no longer experiencing asthma symptoms at the time of the survey. The asthma profile of young adults conceived by IVF appeared to be favourable compared with the general population of the USA. Although few statistically significant results were obtained, low birthweight infants and individuals of a multiple gestation tended to be diagnosed at a later stage and were more likely to be current asthmatics seeking healthcare services than normal-weight infants and individuals of a singleton gestation. Further studies using larger samples and more advanced designs are needed to confirm these preliminary findings. 

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Introduction

Infertility is an important public health issue affecting the lives of many couples in the USA and worldwide. Since 1978, over a million infants have been born to infertile couples as a

result of assisted reproduction technology (Klonoff-Cohen, 2005). IVF is a special type of treatment whereby both oocytes and spermatozoa are handled and fertilization occurs in an artificial environment outside of the reproductive system. Multiple steps are taken in an IVF treatment

cycle; these include ovarian stimulation, oocyte retrieval, fertilization in a liquid medium, embryo selection and embryo transfer into the uterine environment. Scientific evidence remains inconclusive as to whether assisted reproduction is linked to adverse short-term and long-term health effects. Most couples who undergo treatment have pre-existing health problems associated with infertility, and the procedure itself can enhance the risk of birth plurality, which in turn has been linked with preterm delivery and low birthweight infants. While ample evidence linking assisted reproduction technology to preterm deliveries and low birthweight infants exists even in the context of single live births (McDonald et al., 2009), it is unclear whether these birth outcomes are due to parental sub-fertility or characteristics of the procedure itself.

Because assisted reproduction technology is a relatively recent treatment modality for infertility, few studies have evaluated its health effects beyond infancy, childhood and adolescence. Health outcomes that have been evaluated in relation to assisted reproduction technology can be broadly classified as obstetric, perinatal, neonatal, post-neonatal outcomes, chromosomal aberrations, congenital malformations, growth and metabolic disorders and motor, neurological, cognitive and socio-emotional development.

To date, few studies have examined assisted reproduction technology as a putative risk factor for asthma. Asthma is a highly prevalent condition often diagnosed prior to adulthood. Its multi-factorial aetiology has been described elsewhere (Hill and Wood, 2009; Subbarao et al., 2009). In the USA, about 23 million are afflicted with asthma, 6.8 million of whom are children and over half (12 million) have experienced an asthma attack within the last 12 months (NIH, 2009). Preterm delivery and low birthweight have been identified as key risk factors for asthma in a number of studies (Alper et al., 2006; Annesi-Maesano et al., 2001; Linneberg et al., 2006; Metsala et al., 2008; Priftis et al., 2007). The significant relationship between preterm delivery and asthma has been recently established in a meta-analysis of 19 studies (Jaakkola et al., 2006). Because assisted reproduction technology is associated with birth plurality and preterm delivery, it is reasonable to postulate that assisted reproduction technology and asthma may be associated.

The purpose of this descriptive study is to characterize asthma and its associated health outcomes among IVF-conceived young adults. First, the study compared the asthma profile of an IVF population to that of the general population of the USA, using the 2008 Behavioural Risk Factor Surveillance System (BRFSS) as a reference. Second, it examined whether birth plurality and low birthweight played a role in asthma prevalence and associated health outcomes. Given the established link between asthma, preterm delivery and low birthweight, the study postulated that the prevalence of asthma would be increased among IVF-conceived young adults, particularly those who were low birthweight infants or individuals of a multiple gestation. This study was based on a larger cross-sectional survey of young adults (aged 18–26 years) conceived by standard IVF between 1981 and 1990 at a major fertility treatment centre (Beydoun et al., *in press*).

Materials and methods

Study design and setting

This study conducted a cross-sectional evaluation of the first cohort of young adults conceived by IVF at the Jones Institute for Reproductive Medicine (JIRM), the Division of Reproductive Endocrinology and Infertility at Eastern Virginia Medical School (EVMS) in Norfolk, Virginia. The Institutional Review Board at EVMS approved the study with a waiver of informed consent.

Sampling and eligibility

Young adults conceived by standard, or conventional, IVF were recruited and enrolled into the study through their parents. At the time, neither oocyte nor embryo micromanipulation were applied; however, a limited number were conceived through gamete donation or frozen embryos. Arslan et al. (2005) and Riggs et al. (2010) have published reviews of IVF procedures during the first two decades of experience at the study centre. Diagnostic, treatment and outcome data are routinely collected and recorded in a specialized database for all patients seeking IVF at the JIRM. A list of IVF cycles that resulted in a live birth was created and a sampling frame was generated by reconciling this list against a mailing list. The mailing list contains personal data on former JIRM patients, including their names and home addresses. A contact list was created by applying a set of eligibility criteria to the sampling frame. Former patients were included on the contact list if they sought IVF treatment between 1 January 1981 and 31 December 1990 and delivered at least one live-born infant. Former patients with more than one successful IVF cycle were also included on the contact list. Those who were not willing to be contacted, those who had not disclosed method of conception to their IVF offspring and those who had no surviving offspring conceived by IVF were excluded from the contact list. A total of 417 former patients and 560 young adults (out of 816 presumed alive at the time of the survey) met all eligibility criteria.

Recruitment, enrolment and instrumentation

An initial contact letter and two follow-up letters were mass-mailed to former patients on the contact list, i.e. the parents of the IVF-conceived young adults. These letters described study procedures and asked patients to complete and mail an enclosed form in a self-addressed envelope; the form enquired about their willingness to partake in the study by forwarding survey materials to their eligible offspring. To maintain confidentiality, young adults were instructed to contact a third-party key-holder at the JIRM, on a voluntary basis; this contact person was responsible for assigning each young adult a unique identifier and granting them access to the survey instrument. Whereas the contact person had no access to survey responses, investigators had only access to unidentified survey data. At the closing date of the survey, 209 (50.1%) of the former patients had not replied to initial or follow-up letters, 18 (4.3%) were

untraceable and 17 (4.1%) refused to participate, leaving 173 (41.5%) who had forwarded survey materials to eligible young adults. Of 189 eligible subjects who were given a unique identifier, 173 (91.5%) completed the survey by the closing date. Of 146 mothers to the 173 respondents, nine (6.2%) conceived through egg donation and three (2.1%) conceived through sperm donation; seven of the 173 respondents were conceived from frozen–thawed embryos. The estimated response rate was 31%. Whereas respondents ($n = 173$) and non-respondents ($n = 387$) did not differ significantly in terms of age or birth plurality, the proportion of females was considerably higher among respondents compared with non-respondents (56.6% versus 42.6%; $P = 0.002$).

The survey instrument was entirely focused on assessing young adults and no parental data were obtained. A 90-item self-administered questionnaire was used to collect data on demographics, employment, health status, physical development, self-perceptions, anxiety and depression, health behaviours and chronic diseases. This questionnaire was initially developed in a paper-and-pencil format and later converted into an online survey using QuestionPro; the online version was the preferred method of administration (www.questionpro.com).

Asthma profile

Questionnaire items used to evaluate asthma prevalence, frequency and severity were adapted from the BRFSS Codebook (BRFSS, 2008). Initiated in 1984, the BRFSS is an on-going telephone health survey system, tracking health conditions and risk behaviours in the USA. Currently, the BRFSS is conducted by the 50 state health departments as well as those in the District of Columbia, Puerto Rico, Guam and the US Virgin Islands with support from the Centres for Disease Control and Prevention. The BRFSS provides state-specific information about issues of adults (18 years and older) such as asthma, diabetes, healthcare access, alcohol use, hypertension, obesity, cancer screening, tobacco use, nutrition and physical activity.

In this study's survey and the 2008 BRFSS, respondents were asked a screener question that assesses their lifetime experience with asthma, namely 'Have you ever been told by a doctor, nurse or other health professional that you had asthma?' Those who responded affirmatively were asked a battery of questions that assessed age at asthma diagnosis ('How old were you when you were first told by a doctor, nurse or other health professional that you had asthma?'), current asthma status ('Do you still have asthma?'), asthma exacerbations ('During the past 12 months, have you had at least one episode of asthma or an asthma attack?') and asthma-related disability and healthcare utilization ('During the past 12 months, how many times did you see a doctor, nurse or other health professional for a routine check-up for your asthma?', 'During the past 12 months, how many times did you see a doctor, nurse, or other health professional for urgent treatment of worsening asthma symptoms?', 'During the past 12 months, how many days were you unable to work or carry out your usual activities because of your asthma?' and 'During the past 30 days, how often did you take asthma medications (including inhalers) that were prescribed or given to you by a doctor?'). In the 2008 BRFSS, detailed data on adult

asthma history were available for seven states, namely Arizona, District of Columbia, Idaho, Kentucky, Mississippi, North Carolina and Puerto Rico. By contrast, data on lifetime and current asthma status were collected by 37 states.

Because the study sample had few racial/ethnic minorities, the 2008 BRFSS data were restricted to young adults (18–24 years) who were white non-Hispanic. To ensure comparability with the 2008 BRFSS data, the sample of survey respondents was restricted to 157 individuals who were between the ages of 18 and 24 years. Out of 414,509 2008 BRFSS participants, 5339 (1.3%) were white non-Hispanic between 18 and 24 years of age. Of those, 5287 (99%) had known lifetime and current asthma status. Detailed asthma questions were non-standard and therefore only available for a small percentage of lifetime asthmatics.

Covariates

Self-reported birthweight brackets were used to classify survey participants as low birthweight (<2500 g) or normal weight (≥ 2500 g). Birth plurality was assessed by asking survey participants 'Were you an outcome of a single, twin, triplet, quadruplet or more pregnancy?' Other demographic characteristics (age in years; gender; race/ethnicity ('white non-Hispanic or other'); education ('high school or lower' or 'college or higher'); and lifestyle (body mass index

Table 1 Basic characteristics of survey sample ($n = 157$).

Characteristic	n	%
Birth plurality ($n = 156$)		
Singleton	94	60.3
Twin	52	33.3
Triplet	7	4.5
Quadruplet or more	3	1.9
Age (years; $n = 157$)		
18–20	76	48.4
21–24	81	51.6
Gender ($n = 157$)		
Male	70	44.6
Female	87	55.4
Race/ethnicity ($n = 157$)		
White non-Hispanic	154	98.1
Other	3	1.9
Education ($n = 157$)		
High school or lower	42	26.8
College-associate degree	53	33.8
Bachelor-graduate degree	62	39.5
Body mass index (kg/m^2 ; $n = 152$)		
Underweight (<18.5)	0	0.0
Normal weight (18.5–24.9)	83	54.6
Overweight (25–29.9)	53	34.9
Obese (>30)	16	10.5
Smoking status ($n = 156$)		
Current smoker	20	12.8
Ex-smoker	40	25.6
Non-smoker	96	61.5

<18 kg/m², 25–29.9 kg/m² or >30 kg/m²; smoking 'current smoker', 'ex-smoker' or 'non-smoker') were also described.

Statistical analysis

All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). Summary statistics included frequencies and percentages for categorical variables or mean \pm standard deviation (SD) for continuous variables. While analyses of 2008 BRFSS data were conducted taking complex survey design and recommended weighting procedures into account, the survey sample data were analysed assuming simple random sampling. In assessing the role of birth plurality, logistic regression modelling was used to compute OR and their 95% CI.

Results

Demographic, socioeconomic and lifestyle characteristics of the 157 survey respondents are displayed in Table 1. Over half were between 21 and 24 years of age and 55.4% were female. Almost all respondents were white non-Hispanic and nearly three-quarters had achieved a college education or better. In addition, 10.5% of survey respondents were obese and 12.8% reported themselves as current smokers at the time of survey administration. Nearly 24% of respondents were low birthweight and over 39% were individuals of

a multiple gestation; 52 of those were twins, seven were triplets and three were quadruplets.

Asthma characteristics of survey respondents are displayed and compared with the 2008 BRFSS data in Table 2. The lifetime prevalence of asthma in survey respondents was 16.1% and nearly half of ever-diagnosed asthmatics reported no longer having asthma. Survey respondents had similar lifetime and current prevalence rates of asthma compared with the 2008 BRFSS population. Half of the survey respondents (versus 78.0% of the 2008 BRFSS population) received an asthma diagnosis by the age of 10 years. A little over half of the 2008 BRFSS population experienced an asthma episode/attack within the last 12 months compared with only 36.0% of the survey respondents. Whereas the prevalence of routine check-ups for asthma was comparable among asthmatics in the two groups, a larger disparity was seen when addressing other aspects of healthcare utilization pertaining to asthma. Specifically, 47% of 2008 BRFSS asthmatics sought urgent treatment at least once in the last year compared with only 12.0% of asthmatics in the survey sample. Similarly, 33% of 2008 BRFSS asthmatics experienced at least one disability day in the past year due to asthma while only 12.0% of the survey sample reported the same. Almost two-thirds (62.0%) of the asthmatics in the IVF sample reported no medication usage over the past 30 days compared with 46.0% of the 2008 BRFSS population.

Associations of asthma characteristics with birth plurality and low birthweight status are reported in

Table 2 Asthma characteristics: survey sample versus 2008 BRFSS.

Characteristic	Survey sample (n = 157)	2008 BRFSS (n = 5339)
Ever diagnosed with asthma (n)	156	5326
Yes	16.1	17.9
No	83.9	82.1
Still have asthma (n)	156	5287
Yes	8.9	9.6
No	91.1	90.4
Age at diagnosis (n) ^a	24	124
≤ 10 years	50.0	78.0
≥ 11 years	50.0	22.0
Asthma episode or attack (n) ^a	25	71
Yes	36.0	51.7
No	64.0	48.3
Routine asthma check-up (n) ^a	25	71
None	56.0	58.3
1 or more	44.0	41.7
Urgent treatment visit (n) ^a	25	34
None	88.0	53.0
1 or more	12.0	47.0
Negatively impacted days (n) ^a	25	71
None	88.0	67.0
1 or more	12.0	33.0
Medication use per last 30 days (n) ^a	24	69
None	62.0	46.0
1 or more	37.0	54.0

Values are % unless otherwise stated.

BRFSS = Behavioural Risk Factor Surveillance System.

^aAmong individuals who reported lifetime experience with asthma.

Table 3 Associations of asthma characteristics with birth plurality in the survey sample ($n = 157$).

Characteristic	Singleton (n)	Multiple (n)	OR (95% CI)
Ever diagnosed with asthma			
Yes	15	9	0.92 (0.37–2.24)
No	79	52	1.00
Still have asthma			
Yes	7	4	1.14 (0.21–6.37)
No	8	4	1.00
Age at diagnosis ^a			
≤ 10 years	10	3	0.25 (0.04–1.44)
≥ 11 years	5	6	1.00
Asthma episode or attack ^a			
Yes	5	3	1.00 (0.17–5.77)
No	10	6	1.00
Routine asthma check-up ^a			
None	9	4	1.00
1 or more	6	5	1.88 (0.35–9.98)
Urgent treatment visit ^a			
None	13	8	1.00
1 or more	2	1	0.81 (0.06–10.48)
Negatively impacted days ^a			
None	13	8	1.00
1 or more	2	1	0.81 (0.06–10.48)
Medication use per last 30 days ^a			
None	11	4	1.00
1 or more	4	5	3.44 (0.60–19.65)

CI = confidence interval; OR = adjusted odds ratio.

^aAmong individuals who reported lifetime experience with asthma.

Tables 3 and 4, respectively. Clearly, the asthma profile was comparable among outcomes of singleton and multiple gestations and low birthweight and normal-weight infants. While few statistically significant differences were observed, interesting trends were noted. Specifically, ever-diagnosed asthmatics who reported themselves as individuals of a multiple pregnancy were less likely than singletons to have been diagnosed between 0 and 10 years of age (OR 0.25, 95% CI 0.04–1.44) and more likely than singletons to report to at least one routine check-up that was asthma-related (OR 1.88, 95% CI 0.35–9.98) and to have used asthma medications in the last 30 days (OR 3.44, 95% CI 0.60–19.65). Also, ever-diagnosed asthmatics who reported themselves as low birthweight were less likely than their normal-weight counterparts to be diagnosed between 0 and 10 years of age (OR 0.50, 95% CI 0.46–0.49).

Discussion

The link between assisted reproduction technology and chronic disease development through birth plurality and its associated adverse outcomes is biologically plausible but has not yet been fully explored. The fetal origins (Barker, 1991) hypothesis states that fetal undernutrition in middle to late gestation can lead to disproportionate fetal growth, thereby affecting the risk of coronary heart disease later in life. Intrauterine stress to the fetus can also retard growth and constrain lung maturation. A limited sup-

ply of nutrients during fetal life may disrupt metabolism and permanently change cell structure. Infant weight gain is further slowed by bronchitis, pneumonia and whooping cough, which can exacerbate respiratory illnesses in adulthood (Barker, 1991; Barker et al., 1991).

As far as is known, this study is one of few to have specifically examined the relationship between assisted reproduction technology and asthma. A previous study with a mean follow-up time of 7 years has evaluated asthma in relation to assisted reproduction technology; it reported a significant relationship between assisted reproduction technology and asthma hospitalizations after 1 year of life while assessing overall healthcare utilization (Ericson et al., 2002). In a recent study, Cetinkaya et al. (2009) compared the prevalence rates of asthma, atopic dermatitis and allergic rhinitis among 158 children (mean age 4.60 ± 2.14 years) born after IVF conception and 102 children (mean age 5.27 ± 2.8 years) selected as control group; the study showed no increased incidence in asthma or other allergic diseases in children born after IVF conception.

The current study assesses the asthma profile of young adults conceived through IVF. The results suggest a similar likelihood of being ever-diagnosed with asthma in the IVF sample compared with a sub-sample from the 2008 BRFSS. Also, the two populations appeared to have similar asthma prevalence rates at the time of survey administration. The disparity between lifetime and current asthma status among young adults may be an artefact due to erroneous attribution of early-age respiratory symptoms to asthma.

Table 4 Associations of asthma characteristics with birthweight status in the survey sample (*n* = 157).

Characteristic	Birthweight <2500 g	Birthweight ≥2500 g	OR (95% CI)
Ever diagnosed with asthma			
Yes	6	15	1.43 (0.50–4.09)
No	24	86	1.00
Still have asthma			
Yes	2	9	0.33 (0.046–2.43)
No	4	6	1.00
Age at diagnosis ^a			
≤10 years	2	7	0.50 (0.46–0.49)
≥11 years	4	7	1.00
Asthma episode or attack ^a			
Yes	1	6	0.30 (0.028–3.25)
No	5	9	1.00
Routine asthma check-up ^a			
None	3	9	1.00
1 or more	3	6	1.50 (0.22–10.08)
Urgent treatment visit ^a			
None	6	12	1.00
1 or more	0	3	— ^b
Negatively impacted days ^a			
None	6	13	1.00
1 or more	0	2	— ^b
Medication use per last 30 days ^a			
None	3	10	1.00
1 or more	3	5	2.00 (0.29–13.73)

CI = confidence interval; OR = adjusted odds ratio.

^aAmong individuals who reported lifetime experience with asthma.

^bAn OR and its 95% confidence intervals could not be calculated due to the presence of empty cells in the cross-tabulation between the characteristic and birthweight status.

Specifically, early-age diagnosis is often suspect and can be associated with misdiagnosis or diagnosis of symptoms that the child eventually outgrows. Because children conceived by IVF are often closely monitored by their healthcare providers, it is plausible that they would be more susceptible to over-diagnosis than others.

Lifetime asthmatics in the IVF population appear to have fewer asthma episodes/attacks, fewer negatively impacted days, less medication usage and a lower number of doctor visits for urgent care. The convenience sampling procedure performed in this study has an inherent flaw affecting comparability between selected survey participants and the 2008 BRFSS. The relatively low response rate achieved in the current survey, and consequently the self-selection bias, may be partly responsible for the observed differences in asthma characteristics between the two populations. Alternatively, factors that are peculiar to the IVF population may also explain these differences. Whereas the 2008 BRFSS sample consisted of individuals from diverse socioeconomic backgrounds, a high socioeconomic status of the IVF population is assumed; in fact, during this era (1981–1990) when IVF was still a non-routine procedure, insurance companies and other third-party payers did not cover IVF costs, making this procedure less accessible to socioeconomically disadvantaged patients. Accordingly, environmental risk factors for asthma may be more prevalent in the 2008 BRFSS than in the selected IVF population.

While the studied populations differed greatly, had the results shown that the IVF sample had a higher percentage of current asthmatics with much more severe symptoms than the 2008 BRFSS sample, a potential case could then have been made that the IVF procedure or some other common thread relative to the IVF population was responsible for the observed asthma-related disparity. The IVF study population, though, appears to be a much healthier asthmatic subset than expected by the demographics.

The cross-sectional design often limits one from establishing a temporal relationship due to simultaneous assessment of exposures and outcomes. In most cases this hinders all but descriptive analysis. Perinatal studies are exceptions to this rule because it is known that an exposure variable such as birth plurality preceded a postnatal health outcome such as asthma. Although none of the asthma characteristics were found to be significantly related to birth plurality, the observed trends might suggest that IVF-conceived young adults who were the outcome of a multiple gestation were diagnosed with asthma at a later stage compared with singletons; thus, multiples were also more likely to be current asthmatics with recent healthcare-seeking behaviours associated with their asthma.

A major limitation of this study is that the small sample size impedes the ability to detect true associations, as shown by wide confidence intervals. For instance, a positive relationship between birth plurality and prevalent asthma

may still exist and should be further investigated using a larger sample of IVF-conceived offspring. The rather complex, indirect contact procedure used in this study may account for a lessened ability to obtain responses. The ability to directly contact the participants and having at one's disposal an extensively updated contact registry may have served to increase the response rate. The questionnaire may have also been too lengthy and intimidating, leading to agreement to participate but failure to initiate or complete the survey. Preterm delivery, a key risk factor for asthma, could not be ascertained in this study as it was not part of the questionnaire.

There is also the inherent issue of recall problems with any study utilizing self-reported data. Many of the questions addressed detail-specific topics such as age at first diagnosis of asthma. The study was implemented around holiday breaks commonly scheduled by colleges nationwide in the hope that many college-aged children (whether enrolled in school or not) would be heading home for the holidays. This likely served to increase parental pressure for the young adult to participate and complete the study, provide an avenue to attain unknown answers to certain questions via the parents and encompass a time period in which school and/or work would not be weighing down the participant.

While any of the potential studied variables may be associated with asthma, this does not supply evidence supporting a causal relationship between the IVF procedure, these variables and the subsequent onset of asthma. Descriptive analysis alone cannot implicate any potential relationship between IVF and asthma; only potential correlations between perinatal risk factors and asthma in an IVF population.

In summary, the asthma profile of young adults conceived by IVF appeared to be favourable compared with the general US population. Therefore, young adults conceived through IVF may not constitute a high-risk population for asthma. Although birth plurality was not significantly related to asthma characteristics, individuals of a multiple gestation tended to be diagnosed at a later stage and were more likely to be current asthmatics seeking healthcare services than individuals of a singleton gestation. Further studies using larger samples, more advanced designs and a comprehensive assessment of perinatal factors are needed to confirm these preliminary findings. Children conceived through IVF are finally becoming old enough to study long-term disability and chronic conditions and a push for more research into this field is necessary before any valid health claims can be made.

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