




Multigenerational birth cohort study in China: importance, necessity and beyond

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A birth cohort study is an epidemiological study that enrolls a group of people who were born during a specific period of time and follows up with them from the prenatal period to adulthood and even old age. The establishment of a birth cohort study enables the exploration of the etiology of diseases and enriches the understanding and awareness of health status among the reproductive population. Additionally, it provides evidence-based support for the launch of public health policies and programs and thus practically promotes the health care of women and children, facilitating the early prevention of disease in childhood and adulthood [1].

The first birth cohort was established by Miss Ethel Margaret Burnside and a team of midwives and health visitors in the United Kingdom in the early 1900s. They collected records containing unique information on weight at birth and during infancy for all babies born in Hertfordshire between 1911 and 1939, with the aim of improving the survival, health and development of infants in the county [2]. Since then, birth cohort studies have been launched extensively in many developed countries, such as the Netherlands, Denmark, Japan, Norway, and the United States, as well as some low- and middle-income developing countries [3–8].

In China, the establishment of birth cohorts started later than developed countries. The first birth cohort study was established in 1993 and designed to investigate the effect of peri-conceptional folic acid supplementation on offspring health [9]. Subsequently, birth cohort studies such as the Anhui Birth Cohort, the Born in Guangzhou Cohort Study and the Shanghai Birth Cohort have been established, most of which focus on associations between prenatal exposure factors and adverse pregnancy outcomes as well as offspring's long-term health [10–12]. In addition, families with assisted reproductive technology (ART) conception and families with spontaneous conception were enrolled in the China National Birth Cohort, which was established in 2016 with the goal of systematically evaluating the short- and long-term effects of ART-related factors on offspring health and the possible biological mechanisms of those effects [13].

From FOAD to DOHaD

In the late 1980s, Professors David Barker and Clive Osmond noticed that the parts of the United Kingdom that had the fewest healthy babies in the early 1900s were the same areas that had a higher prevalence of heart diseases 60–70 years later; therefore, they hypothesized that poor conditions in early life might lead to heart diseases in adulthood [14]. To investigate this hypothesis, they followed up individuals in the Hertfordshire records and established the Hertfordshire Cohort Study (including the 1920s Cohort and the 1930s Cohort). Studies based on this cohort led to the proposal of the fetal origins of adult disease (FOAD) hypothesis, with the concept that malnutrition during gestation permanently changes and reprograms the body's structure, function and metabolism in a way that increases the risk for coronary heart disease and other adult diseases in later life. In addition to heart disease, Barker et al. also found fetal origins of hypertension, impaired glucose tolerance and other adult diseases [15–18]. Another study using

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data from the Dutch winter famine cohort, which recruited women exposed to the 1944–1945 famine at the end of the second World War, found that fetal undernutrition may be related to an increased risk for insulin resistance, impaired glucose tolerance, high serum cholesterol, coronary heart disease and psychological disorders, which also corroborates the FOAD hypothesis [19].

With the increasing establishment of birth cohorts, more detailed information during pregnancy and early life has been obtained, thus enabling further studies of developmental plasticity. An accumulating body of research indicates that other risk factors, such as maternal nutrition and early life environment, are also related to the occurrence of coronary heart disease, obesity, hypertension, noninsulin-dependent diabetes and other adult diseases [20, 21]. Therefore, the FOAD concept has advanced to the developmental origins of health and disease (DOHaD) theory, which can better reflect both the gestational and postnatal periods. In 2010, the First Thousand Days concept, which refers to the period from conception to the child's second birthday, was formally launched at an international conference on global child undernutrition and further emphasized the importance of this developmental period for improving child health [22]. To date, these theories have helped many countries formulate public health policies and improve child (and population) health.

From nurturing care to human potential

In addition to health and nutrition, stimulation through parenting and educational support during early life has received more attention in recent years. Children with early adversities, including poverty, poor health and nutrition, and insufficient protection, responsive care, and learning opportunities, may not reach their developmental potential [23]. In 2018, the World Health Organization and United Nations International Children's Emergency Fund, in collaboration with some other international organizations, jointly launched the “Nurturing care framework for early childhood development: linking survive and thrive to transform health and human potential” initiative and emphasized the importance of nurturing care, which contained five components: good health, adequate nutrition, security and safety, opportunities for early learning and responsive caregiving [24].

However, longitudinal birth cohorts designed for studies focusing on opportunities for early learning and responsive caregiving are limited. Maselko et al. analysed the data from the Providence, Rhode Island birth cohort of the National Collaborative Perinatal Project; they found that maternal affection at eight months was negatively correlated with distress level in adult offspring, which suggesting that early nurturing and warmth might have long-term protective

effects on mental health [25]. Recently, an analysis of birth cohorts in two middle-income countries (Brazil: 1993 Pelotas Birth Cohort; South Africa: Birth to Twenty Plus Birth Cohort; all data were collected from mothers and offspring) indicated that early nurturing home environments (higher learning opportunities and responsive caregiving) might protect young children from the adverse effects of early adversity on adolescent intelligence quotients [26].

Recent situation in China

Increasing demand for nurturing care

In November 2013, the Chinese government announced the end of the one-child policy and replaced it with a partial two-child policy, which encouraged couples to have two babies if either parent was a singleton. Following this, a universal two-child policy was officially declared in October 2015, and a three-child policy was then launched in August 2021. With the implementation of this series of birth policies, the number of two/three-child families grew, and the demand for nurturing care increased. From the 6th to the 7th national population census, the proportion of a second child in new births has increased from 31.28% to 43.08%, and the proportion of a third or above child has increased from 6.55% to 11.13% [27, 28]. Women giving birth to a second or above child have a lower education level (high school and below, 52.99% in first child; 71.84% in second or above child) and advanced maternal age (≥ 35 years; 7.78% in first child, 21.78% in second or above child), which may increase their pressure for nurturing care [27].

Although the implementation of new birth policies had some effects (the number of a second or above child has increased from 450,194 to 657,291 according to the 6th and the 7th national population census; the total birth rate in 2014 and 2016 were higher than that in 2013 and 2015, respectively), the total birth rate has continued to decrease in recent years (from 2016 to 2021: 13.57‰ to 7.52‰) [27, 28]. The reason for this phenomenon is complex. For example, the decrease in women of childbearing age, the change in fertility culture, and the effects of the COVID-19 pandemic may all influence people's fertility desire and thus decrease the birth rate [29]. Additionally, the increasing demand for nurturing care, which includes expensive costs and high demands for time and energy, might also be an important reason for the decrease. As reported by the National Development and Reform Commission of China, concern over unattended infants might be the primary reason for the lower birth rate. However, longitudinal large-scale studies exploring the influencing factors of and potential solutions for fertility desire change and birth rate decrease are limited. The involvement of grandparents in nurturing care may help to share the cost of child rearing,

but its effects on offspring's early development remain to be further studied.

Involvement of grandparents in nurturing care

In the first few years of life, parents, intimate family members and caregivers are the closest to the child and the best providers of nurturing care. A number of children are raised by their grandparents due to parents' lack of time, energy and money [30, 31]. The proportion of these children is relatively small in other countries, such as South Korea (6%) and the United States (2.6%) [30, 31]. However, in China, the phenomenon is particularly prevalent. Although most previous studies had limited sample sizes and the participants were from different areas, all of them reported a high proportion of grandparents involved in childcare, ranging from 58% to 82.3% [31–35]. Moreover, the care intensity of grandparents is higher in rural areas as a result of population migration [34, 35]. In addition to the traditional ideas in China that indicate grandparents' responsibility for helping their children in child caring, the process of urbanization and implementation of new birth policies, accompanied by an increasing migrant population and demands for nurturing care, have also contributed to the increasing involvement of grandparents in nurturing care.

Accumulating evidences have indicated that grandparental nurturing care may affect offspring's physical and neuropsychological development and result in overweight and/or obesity, developmental delays, behavioral issues, attention deficit hyperactivity disorder and so on [36–41]. A nationally representative cross-sectional survey in the United States also reported that children in grandparent-led households had increased physical health conditions, as well as emotional, mental, and developmental health conditions [42]. However, most of these studies did not recruit grandparents and lacked detailed information about the grandparents (such as age, education, disease history and so on) and the early developmental environment (such as opportunities for early learning and responsive caregiving).

Unequal developmental environment of left-behind children and migrant children

With the great social processes of urbanization and modernization, vast numbers of employment opportunities have been created in urban areas, which has led to the migration of the labor force population and an increase in left-behind children (LBC), who are left behind by their parents in their hometown, and migrant children, who migrate together with their parents. The problem of LBC and migrant children care has always been a discussion hotspot in China. According to data from the 7th National Population Census, there are approximately 58.91 million LBC and 71.09 million migrant

children, which accounts for more than 40% of the total child population in China [27].

Most LBC, especially those in rural areas, are left behind by both parents and raised only by grandparents [35, 43]. Normally, they may live in a poorer developmental environment and have worse developmental outcomes, such as a higher risk of social-emotional problems, developmental delays, lower IQ [35, 44, 45]. However, most previous studies on the early development of LBC are cross-sectional studies and have limited sample sizes or lack detailed information on grandparents. Some parenting intervention programs slightly improved children's development outcomes in treatment households and indicated the feasibility of promoting children's early development by improving the developmental environment among LBC, but the sample sizes were also small [46, 47]. In addition, most of the existing policies focusing on LBC target those in rural areas. The situation of urban LBC is easy to ignore, although the proportion continues to grow with further urbanization. According to data from the 7th National Population Census and the Ministry of Education, the proportion of urban LBC accounted for about 51.8% of the total number of LBC in the compulsory education phase in 2020.

Although migrant children can receive more nurturing care from their parents, they may have difficulty obtaining adequate and high-quality resources since they are a nonresident population. The household registration system (Hukou system) ties rights and benefits for individuals to their Hukou status and location. Thus, migrant families typically cannot receive the same resources (e.g., medical and educational resources) as local urban residents. On the other hand, migrant children may experience more early adversities, such as prejudice and discrimination from local people [48].

Therefore, future studies focusing on the unequal early developmental environment of LBC and migrant children, as well as their specific demands for nurturing care, are necessary to provide evidence for the proposition of specific policies and services to provide caregivers with adequate time and resources for nurturing care.

Limited multigenerational cohort studies designed for nurturing care

There are a number of multigenerational birth cohorts being established around the world, most of which are aimed at intergenerational influences of genetics, epigenetics and lifestyle factors rather than the influences of a nurturing care environment [49–52]. Detailed information about several well-known multigenerational birth cohorts is shown in Table 1. In 2014, a feasibility study conducted for the Illawarra Born study collected information

Table 1 Existing multigenerational birth cohort studies

Cohort studies	Study design	Country	Recruitment duration	Participants	Information	Biological samples
The Lifeways Cross-Generation Study	Prospective cohort	Ireland	2001–2002	1124 mothers, 1094 babies, 330 fathers, 707 grandparents with questionnaires and 958 with clinical exams	General health, current and past GMS eligibility, lifestyle habits, changes in diet during pregnancy including the taking of supplements, food frequency questionnaire, clinical data	Not collected, except for grandparents with the option of giving a blood sample at baseline survey for testing
The Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study	Prospective cohort	Japan	2013–2017	22,493 mothers, 23,143 newborns, 9459 siblings of newborns, 8823 fathers, 8058 grandparents, 78 great-grandparents, 1475 extended families	Sociodemographic factors, lifestyle habits, medical history, physiological measurements, and magnetic resonance imaging	Blood, urine, saliva, dental plaque, and breast milk
Avon Longitudinal Study of Parents and Children Generation 2	Prospective cohort	England	2012–2018	810 offspring from 548 families where at least one parent was newborn in ALSPAC, of whom 389 (48%) were recruited during their mother's pregnancy	Socioeconomic, lifestyle, clinical, anthropometric and biological data	Blood (including cord-blood), urine, placental tissue, meconium and feces
The Illawarra Born study	Feasibility study; Prospective cohort	Australia	2014	41 mothers, 40 newborns, 8 fathers, 8 grandmothers	Mental health, personality, attachment, bonding and relationships, quality of life, alcohol consumption, childbirth and parenting, diet, motor development	Blood, urine, feces, cheek swab, exhaled gas, saliva
The Uppsala Birth Cohort Multigeneration study	Retrospective cohort	Sweden	2005	14,193 original cohort members, their 21,070 biological children, 37,234 grandchildren and 12,900 great grandchildren born up to 2002	population-based registration data, social and early life characteristics and deaths before 1961 for the original cohort born between 1915 and 1929 and their parents	Not collected

GMS General Medical Card Services, ALSPAC Avon Longitudinal Study of Parents and Children

on parenting and aimed to make scientific discoveries associated with improving health and wellbeing across the lifespan [53]. However, only mothers were asked to complete the parenting questionnaires. Furthermore, there are no multi-generationally designed birth cohorts in China, although the Born in Guangzhou Cohort Study has recruited a few maternal grandmothers since 2018.

Therefore, our group aims to establish a large-scale multi-generationally driven birth cohort named the Zhejiang University Birth Cohort, highlighting the increasing demand of nurturing care, the higher involvement of grandparents in childcare and unequal developmental environment of left-behind children and migrant children in China. Detailed information on the nurturing care demands of households, including those with different numbers of children, different rearing patterns or different populations, including LBC and migrant children in rural and urban areas, will be collected in three generations. With these data, our group aims to (1) investigate the association between grandparental involvement in nurturing care and early childhood development; (2) explore potential methods for increasing fertility desire; (3) explore the specific early developmental environment and nurturing care demand of different populations; (4) provide evidence for the formulation of policies and programs to promote early childhood development and to optimize the allocation of education, health and other resources.

In conclusion, with data from birth cohorts, previous studies have corroborated the DOHaD theory and emphasized the importance of the first thousand days of a child's life and nurturing care. However, longitudinal multigenerational data on nurturing care are limited although a significant number of children are raised by their grandparents in many countries, especially China. Considering the increasing demand for nurturing care, the high proportion of grandparental involvement in childcare and the unequal developmental environment of LBC and migrant children, it is necessary to establish a multigenerational birth cohort in China. Therefore, our group will establish the Zhejiang University Birth Cohort, which aims to explore potential approaches to address current situations in China.

Author contributions SN and WH contribute equally as co-first authors. QS and SZ contribute equally as senior and the corresponding authors. SN, WH, QS and SZ contributed to study design and planning. SN, WH and SZ drafted the manuscript. SN, WH, JZ, FY, GB, DL, WX, JL, QS and SZ contributed to the literature analysis and search, and revised the manuscript. All the authors have read and approved the final manuscript.

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Data availability Not needed.

Declarations

Conflict of interest The authors declare that they have no conflict of interest. Qiang Shu is the Co-Editor-in-Chief for *World Journal of Pediatrics*. The paper was handled by the other Editor. Qiang Shu was not involved in the journal's review of, or decisions related to this manuscript.

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