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Prospective investigation of folic acid supplements before and during early pregnancy and paediatric and adult cancers in the Chinese children and families cohort: a pilot study in a sample of rural and urban families

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ABSTRACT

Objective To determine the feasibility of long-term prospective follow-up and ascertainment of cancer in offspring and mothers from the 1993–1995 Chinese Community Intervention Program that provided folic acid supplements before and during early pregnancy to reduce neural tube defects.

Design Feasibility pilot study for a prospective cohort study.

Setting Families residing during 2012–2013 in one rural and one urban county from 21 counties in 3 provinces in China included in the Community Intervention Program campaign.

Participants The feasibility study targeted 560 families, including 280 from the rural and 280 from the urban county included in the large original study; about half of mothers in each group had taken and half had not taken folic acid supplements.

Intervention The planned new study is observational.

Primary and secondary outcome measures Primary: incidence of paediatric cancers in offspring; secondary: other chronic diseases in offspring and chronic diseases in mothers

Results Only 3.4% of pilot study families could not be found, 3.9% had moved out of the study area and 8.8% refused to participate. Interviews were completed by 82% of mothers, 79% of fathers and 83% of offspring in the 560 families. Almost all mothers and offspring who were interviewed also participated in anthropometric measurements. We found notable urban–rural differences in sociodemographic and lifestyle characteristics of the parents, but fewer differences among the offspring. In eight catchment area hospitals, we identified a broad range of paediatric cancers diagnosed during 1994–2013, although paediatric brain tumours, lymphomas and rarer cancers were likely under-represented.

Conclusions Overall, 20 years after the original Community Intervention Program, the pilot study achieved high levels of follow-up and family member interview participation, and identified substantial numbers of paediatric malignancies during 1994–2013 in catchment area hospitals. Next steps and strategies for overcoming limitations are described.

Strengths and limitations of this study

- ► In the pilot study, high proportions of Chinese Community Intervention Program (CIP) mothers, fathers and offspring were traced, identified and participated in interviews and anthropometric measurements.
- ► Incomplete ascertainment of incident paediatric cancers in the CIP offspring is likely in the absence of long-standing population-based cancer registries of high quality in the geographic region where the intervention was carried out.
- ► Reduction of the small proportion of the CIP pilot study subjects who could not be traced or identified, or would not participate in interviews or anthropometric measurements will be challenging, particularly for those pilot study offspring (and parents) who have moved out of the CIP catchment area.

INTRODUCTION

Environmental factors and gene–environment interactions during the periconceptional, prenatal and early-life periods are increasingly linked with cancer and other serious diseases during childhood, adolescence and adulthood, but research is limited and mechanisms are poorly understood.[1 2] Support for the in utero origin of paediatric leukaemia, mostly acute lymphoblastic leukaemia, has been provided by observations on twins showing that the chromosomal rearrangements seen in leukaemia cases could occur in utero, coupled with work demonstrating that certain chromosomal translocations are present in the blood spot cards of children who later developed childhood acute lymphoblastic leukaemia with the same translocations.[3] The only established risk factors for paediatric cancer (eg, ionising radiation, a few genetic or congenital syndromes and birth weight)[4] explain <20% of occurrence.[5 6] Modest increased[7–10] or reduced risks[11 12] have recently been linked with other exposures in pooled paediatric leukaemia case–control studies. Prospects for prevention are limited to avoidance of ionising radiation or high birth weight, although more recently periconceptional folic acid (FA) supplements have been linked with reduced risks in a large pooled analysis.[11] However, results for the association of periconceptional or prenatal FA supplements and paediatric leukaemia have been inconsistent in individual studies, and these inconsistencies and the modest associations observed in the pooled analysis may be due in part to differential or inaccurate long-term recall,[13 14] selection bias[15] and declining participation rates, and growing socioeconomic differences between control and case subjects.[16–18] Prospective large epidemiological studies could overcome many of these limitations.

A unique opportunity to evaluate the potential role of FA supplements before and during early pregnancy in reducing risk of paediatric leukaemia in offspring was identified 20 years after a 1993–1995 Community Intervention Program (CIP) in which FA supplements before and during early pregnancy were provided in 21 Chinese counties to reduce neural tube defects (NTD). Among offspring of 130 142 women who took 400 µg FA supplements compared with offspring of the 117 689 women who did not take FA supplements, there was a 79% and 41% reduction in the prevalence of NTD in high (northeast) and lower (southeast) rate regions, respectively.[19] Extensive information had been collected during 1993–1995 on maternal sociodemographic, lifestyle, reproductive, medical conditions and treatments, occupational and other factors during the periconceptional and prenatal periods, and on offspring during the early neonatal period.

We conducted a pilot study to assess the feasibility of: (1) establishing a large cohort (designated the Children and Families Cohort Study (CFCS)) from the CIP families for planned prospective epidemiological studies evaluating paediatric leukaemia and other health outcomes in offspring and mothers; (2) collecting data from two generations of family members by interview and anthropometric measurements; and (3) identifying and validating paediatric cancers diagnosed during 1994–2013 in the CIP catchment area among children who are potentially eligible CIP offspring.

METHODS

Study team organisation and approvals

In 2012–2013, investigators from the Chinese Center for Disease Control and Prevention (China CDC), US Centers for Disease Control and Prevention (US CDC), the US National Cancer Institute (NCI), the Maternal and Child Health (MCH) Hospital leaders of each county and clinicians of the hospitals selected for identification of paediatric cancers conducted data collection. The protocol was approved by the Chinese provincial, city, and county health bureaus, county MCH hospitals and other participating hospitals, and by the Chinese and US CDCs and US NCI ethics review committees (see details in Ethics Approval section following the Discussion).

Study sample

Five hundred CIP families were targeted from two CIP geographic regions, for example, a rural county in the northeast and an urban county in the southeast. From the pregnancy-monitoring registration system, 280 families from each county were selected with eligibility criteria including: (1) mother resided and underwent a premarital or prenatal physical examination in the specified county during 1993–1995; (2) the pregnancy resulted in a live, single birth in the county by December 1996; (3) sex of the infant was known and (4) high-quality data on maternal use of FA supplements before and during the pregnancy were available.

Tracing and contacting families

County MCH staff verified the names, vital status, current addresses and phone numbers of eligible mothers and children selected by comparing the lists with township and village health service and New Rural Cooperative Insurance rosters. To improve recruitment, the county-level MCH, township hospital, village or community health service centre physicians, assisted by the village development and community/street committee staff, made initial contact with the families.

A letter describing the study purpose, questionnaire topics, physical measurements, confidentiality, benefits, potential risks, incentives and opportunity to opt out of all or part of the data collection was mailed or delivered in person. After letter delivery, the village or Township doctor contacted the mother/caretaker to answer questions and arranged a home visit where consent was obtained.

Interviewer training

After a didactic 2-day training, interviewers practised questionnaire administration and taking anthropometric measurements. The training concluded with instructions on manual review and data editing. Approximately 1 month later, supervisory Chinese CDC staff again evaluated staff and retrained as needed.

Data collection: questionnaires

One of two maternal questionnaires assessed family residential characteristics and maternal sociodemographic characteristics, lifestyle, reproductive and medical history, and job history. If the child resided with a caretaker, a modified shorter questionnaire was administered. A second maternal/caretaker questionnaire asked about the offspring's date of birth, vital status, history of cancer or birth defects, diagnosis of autism, developmental milestones, highest level of education and job history.

The offspring's questionnaire asked date of birth, self-rating of physical health, source of medical care, number of non-routine health visits in the past 12 months, cigarette smoking and secondhand smoke history, use of alcohol and history of pubertal changes.

The father's questionnaire inquired about date of birth, education, marital status, job history, smoking and secondhand smoking, alcohol use and medical history.

Other data collection (results reported separately)

After the interviews, offspring and mothers were invited to participate in anthropometric measurements at the Township hospitals. At the end of questionnaire and anthropometric measurements data collection, the participants received appreciation certificates and incentives. A letter was also provided indicating that the participant might be contacted for a second study to assess diet, nutrition, physical activity and ultraviolet radiation exposure.

Identification and validation of paediatric cancer cases

In consultation with hospitals and community leaders, eight hospitals providing different levels of services were selected from study regions and major cities near to the catchment area where CIP children might have been referred for diagnosis and treatment of paediatric cancer. A workshop was held with experts in paediatric haematology, oncology and neurosurgery from these hospitals to develop the methods for identification and validation of the paediatric cancer outcomes.

The medical record review process included: (1) searching for medical records to identify all paediatric patients with cancer born during 1994–1996 who were diagnosed and/or treated during 1994–2013; (2) developing a list of all potentially eligible patients (born during 1994–1996 in the 21 counties included in the CIP or, if no specific place of birth was listed, those born in the three provinces in which the 21 counties were geographically located); (3) obtaining and abstracting medical records of these patients; and (4) independent reviewing of the abstract forms by two clinical experts with resolution of differences through discussion to determine a final diagnosis. For quality control purposes, each hospital was visited at least once by China CDC staff to evaluate procedures. In the absence of re-identification of the entire CIP cohort and comprehensive population-based cancer registries, it was not possible to link the paediatric cancer cases identified in hospitals with the cohort.

Data management

A data management training workshop was held in Beijing for China CDC staff followed by a detailed review and editing of the data collected. All forms were coded, checked, entered twice and data verified for accuracy. Range and logic sequences were verified against original paper forms and corrections made as required.

Statistical analysis

In data analysis conducted during 2016–2017, cross-tabulation was used to evaluate the distribution of demographic, socioeconomic, lifestyle, developmental and medical history characteristics by county. Fisher's exact tests were used to test for urban versus rural geographic differences by covariates among mothers, offspring and fathers.

Subjects and public involvement

Subjects and the public were not involved in development of the research question, the study design, determination of the outcome measures to be studied, recruitment or conduct of the study. Subjects were informed about results of anthropometric measures and blood chemistry laboratory tests (methods for the laboratory test components of a second pilot study are reported elsewhere). Subjects also received physical activity monitors at the end of the physical activity monitoring component of the second pilot study (methods reported elsewhere).

If the full-scale study is funded, the findings would be shared with the subjects, public health officials and medical professionals through newsletters and other types of communication.

RESULTS

Of the 560 families selected for the pilot study, only 3% (2% in the rural and 5% in the urban centre) could not be found, 4% of families reportedly moved away (6% in the rural and 2% in the urban centre) and 9% (8% in the rural and 9% in the urban centre) refused to be contacted (table 1). Overall, 82% of mothers, 79% of fathers and 83% of offspring completed interviews of the 560 families selected. Among the 469 families (84% of the 560 selected) targeted for interviews (after excluding those who could not be found, had moved away or had refused to be contacted), the interview participation was very high, for example, 98% of mothers, 95% of fathers and 99% of offspring. Almost all mothers and offspring who were interviewed also participated in the anthropometric measurements (table 1). The proportion of mothers contacted who took FA supplements (49% in the rural centre and 52% in the urban centre) was similar to the 50% in each centre who took FA in the samples originally selected.

Nearly half of urban families resided 10 or fewer years in their current home, whereas 90% of rural families had lived >10 years in the current home (table 1). More than 93% of rural and urban families owned their current home. Close to half of the urban families compared with 21% of rural families had five or more persons recently residing in their residence.

Table 1 Population targeted for pilot study, description of participants, reasons for non-participation, and residential and sociodemographic characteristics of participating families

	Rural area N (%)	Urban area N (%)	Both areas N (%)	P value*
Population targeted, description of participants and reasons for non-participation in pilot study				
Number of families selected for pilot	280	280	560	
Families selected but not included	46 (16.4%)	45 (16.1%)	91 (16.3%)	
Reason not included				
Moved away	17 (6.1%)	5 (1.8%)	22 (3.9%)	
Not found	6 (2.1%)	13 (4.6%)	19 (3.4%)	
Refused	23 (8.2%)	26 (9.3%)	49 (8.8%)	
Mother deceased	0	1 (0.3%)	1 (0.1%)	
Families targeted for interviews†	234 (83.6%)	235 (83.9%)	469 (83.8%)	
Mothers who consented among families targeted for interview	229 (97.9%)	231 (98.3%)	460 (98.1%)	
Mothers				
Completed interview‡	229 (81.8%)	231 (82.5%)	460 (92.1%)	
Physical measurements§	228 (99.6%)	230 (99.6%)	458 (99.6%)	
Fathers				
Completed interview‡	232 (82.9%)	212 (75.7%)	444 (79.3%)	
Children				
Completed interview‡	233 (83.2%)	229 (81.8%)	462 (82.5%)	
Physical measurements§	231 (99%)	229 (100%)	460 (99.6%)	
Caretakers				
Completed interview¶	6	9	15	
Residential and sociodemographic characteristics of participating families				
Number of years at current home				
≤10	23 (10%)	111 (48%)	134 (29%)	<0.0001
11–19	138 (59%)	76 (33%)	214 (46%)	
20+	71 (31%)	45 (19%)	116 (25%)	
Unknown	0	1 (0.4%)	1 (0.2%)	
Own or rent home				
Own	224 (97%)	216 (93%)	440 (95%)	0.0572
Rent	7 (3%)	17 (7%)	24 (5%)	
Unknown	1 (0.4%)	0	1 (0.2%)	
Highest number of persons residing in residence in the past year				
≤3	100 (43%)	97 (42%)	197 (42%)	<0.0001
4	83 (36%)	26 (11%)	109 (23%)	
≥5	49 (21%)	110 (47%)	159 (34%)	

*Fisher's exact test for rural versus urban differences.
†Targeted for interviews were those who had not moved away, could be found, did not refuse or mother not deceased.
‡Per cents shown are the proportion completing interviews of those selected for the pilot study.
§Per cents are the proportions who completed physical measurements of those who were interviewed.
¶If mother not available, caretaker information was used.

Urban mothers were younger at the age of marriage registration, birth of the CIP offspring, and at the age of current interview completion (table 2). Rural mothers reported less education, held fewer jobs and a slightly higher proportion were married compared with urban mothers. Almost none of the rural and urban mothers reported smoking cigarettes. Rural mothers (43%) were somewhat more likely than urban mothers (33%) to report being exposed to secondhand smoke during their pregnancies for ≥3 days per week. Rural mothers

Table 2 Maternal sociodemographic, lifestyle and reproductive characteristics, Chinese CFCS questionnaire, 2013

Characteristics	Rural area n=229 (%)	Urban area n=231 (%)	Both areas n=460 (%)	P value*
Age at CIP enrolment/marriage registration				
≤22	84 (37%)	126 (55%)	210 (46%)	0.0004
23–24	66 (29%)	59 (26%)	125 (27%)	
≥25	79 (34%)	46 (20%)	125 (27%)	
Age at first birth				
≤23	88 (38%)	132 (57%)	220 (48%)	<0.0001
24–25	58 (25%)	57 (25%)	115 (25%)	
≥26	83 (36%)	42 (18%)	125 (27%)	
Age at CFCS interview completion				
≤39	70 (31%)	116 (50%)	186 (40%)	<0.0001
40–41	72 (31%)	67 (29%)	139 (30%)	
≥42	87 (38%)	48 (21%)	135 (29%)	
Highest level of education				
None	3 (1%)	1 (0.4%)	4 (1%)	<0.0001
Some or all elementary school	42 (18%)	17 (7%)	59 (13%)	
Completed middle school	144 (63%)	143 (62%)	287 (62%)	
Completed high school/technical school	39 (17%)	46 (20%)	85 (18%)	
Completed some or all college/university	1 (0.4%)	24 (10%)	25 (5%)	
Current marital status				
Married	227 (99%)	216 (94%)	443 (96%)	0.0002
Widowed	2 (1%)	1 (0.4%)	3 (1%)	
Divorced	0	12 (5%)	12 (3%)	
Other	0	2 (1%)	2 (0.4%)	
Current number of jobs after completed school				
None	0	1 (0.4%)	1 (0.2%)	<0.0001
1	158 (69%)	21 (9%)	179 (39%)	
2	48 (21%)	68 (29%)	116 (25%)	
3+	23 (10%)	141 (61%)	164 (36%)	
Smoking/secondhand smoke				
Never smoked cigarettes regularly	227 (99%)	230 (100%)	457 (99%)	0.6225
Exposed to secondhand smoke at home >10 years before age 20	91 (40%)	79 (34%)	170 (37%)	0.2872
Exposed to secondhand smoke at home >10 years after age 20	125 (55%)	122 (53%)	247 (54%)	0.5299
Exposed to secondhand smoke during CIP pregnancy for three or more days per week	99 (43%)	77 (33%)	176 (38%)	0.0689
Child exposure to secondhand smoke before age 5 years				
None	101 (44%)	105 (45%)	206 (45%)	0.0088
<3 days per week	22 (10%)	43 (19%)	65 (14%)	
3+ days per week	103 (45%)	80 (35%)	183 (40%)	
Unknown	3 (1%)	3 (1%)	6 (1%)	
Ever drink alcohol				
No/less than once per month	226 (99%)	213 (92%)	439 (95%)	0.0012
Yes	3 (1%)	18 (8%)	21 (5%)	

Continued

Table 2 Continued

Characteristics	Rural area n=229 (%)	Urban area n=231 (%)	Both areas n=460 (%)	P value*
Age menstrual periods started, years				
12–13	29 (13%)	47 (20%)	76 (17%)	0.0497
14–15	120 (52%)	122 (53%)	242 (53%)	
16+	78 (34%)	62 (27%)	140 (30%)	
Unknown	2 (1%)	0	2 (0.4%)	
Number of pregnancies				
1	68 (30%)	37 (16%)	105 (23%)	0.0002
2	95 (41%)	86 (37%)	181 (39%)	
3	53 (23%)	74 (32%)	127 (28%)	
4+	13 (6%)	34 (15%)	47 (10%)	

*Fisher's exact test for rural versus urban differences.
CFCS, Children and Families Cohort Study; CIP, Community Intervention Program.

(45%) were more likely than urban mothers (35%) to report that their offspring had been exposed to secondhand smoke ≥ 3 days per week before age 5 years. Few of the mothers (5% overall, 8% urban versus 1% rural) reported drinking alcohol. Rural mothers were more likely to report onset of menstrual periods at older ages, and 30% of rural compared with 16% of urban mothers reported only one pregnancy.

Rural fathers were older at the time of marriage registration, birth of their offspring and at the current interview compared with urban fathers (table 3). Rural fathers reported less education and fewer jobs compared with urban fathers. A higher proportion of rural (33%) compared with urban (19%) fathers reported never smoking, although rural fathers were more likely than urban fathers to be exposed to secondhand smoke for over 10 years before age 20. Urban (75%) compared with rural (60%) fathers were more likely to be currently smoking. Use of alcohol was similar between rural (63%) and urban (65%) fathers, but a somewhat higher proportion of urban (61%) than rural (57%) fathers reported alcohol use for ≥15 years.

Urban versus rural differences in sociodemographic factors were less apparent among offspring (table 4). The two groups were similar in birth year, age at interview, and sex distribution, but somewhat more urban than rural offspring reported living with their parents. Most in each group were full-time students, but urban offspring were more likely to report attending trade or technical school. Most offspring in both groups reported never smoking cigarettes regularly; a somewhat higher proportion of urban than rural offspring reported secondhand smoke exposure at home for ≥1 days per week and alcohol use for ≥1 days since birth.

Eight hospitals selected included county and provincial hospitals, children's medical centres and referral hospitals in the nearby cities of Beijing (treating brain tumours), Tianjin (haematological disorders) and Shanghai (paediatric oncology) to which children would have been referred for definitive diagnosis and treatment of paediatric cancer (table 5). A broad range of incident paediatric malignancies and related disorders were identified in the eight hospitals; of the total cancers, 77% were designated by type and 23% were unspecified (table 4). Of the 137 paediatric cancers identified, 37% were leukaemias. Only 10% (13/137) of the paediatric neoplasms were brain tumours and 7% (9/137) were lymphomas, although similar numbers were identified in the earlier (1994–2003) and later (2004–2013) time periods. No retinoblastomas were identified.

DISCUSSION

In the pilot study of 580 CIP families, we located all but 3.4% of the families and only 8.7% refused to participate. Overall, 82% of mothers, 79% of fathers and 83% of offspring selected of the 560 families chosen completed interviews. More than 90% of those who agreed to be contacted completed interviews, and 99% of the mothers and offspring completed anthropometric measurements. We found notable differences in sociodemographic and lifestyle characteristics between rural and urban parents, but fewer differences in offspring. We identified a broad range of incident (1994–2013) paediatric cancers in the diverse hospitals, but there appeared to be incomplete ascertainment of paediatric brain tumours, lymphomas and certain others (retinoblastoma), and 23% were of unspecified subtype.

Supporting our findings of notable rural versus urban differences in parents, data since the 1990s from the National Bureau of Statistics of China have consistently shown significant differences between rural and urban areas in gross domestic product (GDP), per capita income and educational attainment.[20] The two pilot study centres differed significantly in geography and urbanicity (rural northeast vs urban southeast regions), GDP

Table 3 Paternal sociodemographic and lifestyle characteristics, Chinese CFCS questionnaire, 2013

Characteristics	Rural area n=232 (%)	Urban area n=212 (%)	Both areas n=444 (%)	P value*
Age at CIP enrolment/marriage registration				
≤22	77 (33%)	85 (40%)	162 (36%)	0.0030
23–24	56 (24%)	69 (33%)	125 (28%)	
≥25	99 (43%)	58 (27%)	157 (35%)	
Age at birth of child				
≤23	71 (31%)	91 (43%)	162 (36%)	0.0002
24–25	59 (25%)	67 (32%)	126 (28%)	
≥26	102 (44%)	54 (25%)	156 (35%)	
Age at CFCS interview completion				
≤39	58 (25%)	77 (36%)	135 (30%)	0.0038
40–41	68 (29%)	69 (33%)	137 (31%)	
≥42	106 (46%)	66 (31%)	172 (39%)	
Highest level of education				
None	1 (0.4%)	0	1 (0.2%)	<0.0001
Some or all elementary school	43 (19%)	16 (8%)	59 (13%)	
Completed middle school	153 (66%)	125 (59%)	278 (63%)	
Completed high school/technical school	32 (14%)	49 (23%)	81 (18%)	
Completed some or all college/university	3 (1%)	22 (10%)	25 (6%)	
Number of jobs after completed school				
1	146 (63%)	28 (13%)	174 (39%)	<0.0001
2	63 (27%)	65 (31%)	128 (29%)	
3+	23 (10%)	119 (56%)	142 (32%)	
Currently smoking cigarettes				
Never smoked	77 (33%)	40 (19%)	117 (26%)	0.0008
No	16 (7%)	13 (6%)	29 (7%)	
Yes	139 (60%)	159 (75%)	298 (67%)	
Secondhand smoke				
Exposed to secondhand smoke at home >10 years before age 20	103 (44%)	73 (34%)	176 (40%)	0.0275
Exposed to secondhand smoke at home >10 years after age 20	53 (23%)	56 (26%)	109 (25%)	0.7922
Use of alcohol				
No/less than once per month	86 (37%)	74 (35%)	160 (36%)	0.6924
Yes	146 (63%)	138 (65%)	284 (64%)	
Use of alcohol in years				
Never	86 (37%)	74 (35%)	160 (36%)	<0.0001
<15	1 (0.4%)	2 (1%)	3 (1%)	
15–19	8 (3%)	36 (17%)	44 (10%)	
20+	125 (54%)	94 (44%)	219 (49%)	
Unknown	12 (5%)	6 (3%)	18 (4%)	

*Fisher's exact test for rural versus urban differences.
CFCS, Children and Families Cohort Study; CIP, Community Intervention Program.

(higher in southeast), principal industry (agricultural in the northeast vs high technology industry in the southeast) and greater in-migration in the southeast. Recently, household income, education and health status have been shown to account for the lower use of preventive care services by rural compared with urban residents.[21]

Table 4 Offspring sociodemographic and lifestyle characteristics, Chinese CFCS questionnaire, 2013

Characteristics	Rural area n=233 (%)	Urban area n=229 (%)	Both areas n=462 (%)	P value*
Year of birth				
1994	67 (29%)	70 (31%)	137 (30%)	0.7667
1995	106 (45%)	96 (42%)	202 (44%)	
1996	60 (26%)	62 (27%)	122 (26%)	
Unknown	0	1 (0.4%)	1 (0.2%)	
Age at interview completion, years				
<16	88 (38%)	82 (36%)	170 (37%)	0.5264
16	93 (40%)	102 (45%)	195 (42%)	
17+	52 (22%)	44 (19%)	96 (21%)	
Unknown	0	1 (0.4%)	1 (0.2%)	
Sex				
Female	120 (52%)	112 (49%)	232 (50%)	0.6418
Male	113 (48%)	117 (51%)	230 (50%)	
Living arrangements				
Living with parents	211 (91%)	221 (97%)	432 (94%)	0.0001
Living with grandparents or other adult guardian	1 (0.4%)	3 (1%)	4 (1%)	
Other	15 (6%)	0	15 (3%)	
Unknown	6 (2.6%)	5 (2.2%)	11 (2.4%)	
Current activity: school, work, other				
Full-time student	215 (92%)	208 (91%)	423 (92%)	0.2205
Working part-time and attending school part-time	0	3 (1%)	3 (1%)	
Working	6 (3%)	3 (1%)	9 (2%)	
Not working and not attending school	7 (3%)	10 (4%)	17 (3.7%)	
Unknown	5 (2%)	5 (2.4%)	10 (2.2%)	
Highest level of education				
Junior high school	43 (18%)	18 (8%)	61 (13%)	<0.0001
Senior high school	123 (53%)	94 (41%)	217 (47%)	
Trade or technical school	49 (21%)	99 (43%)	148 (32%)	
Unknown	18 (8%)	18 (8%)	36 (8%)	
Ever smoked cigarettes regularly				
No	223 (96%)	215 (94%)	438 (95%)	0.4085
Yes	10 (4%)	14 (6%)	24 (5%)	
Number of days exposed to secondhand smoke where you live in past week				
0	158 (68%)	143 (62%)	301 (65%)	0.0269
1–4	33 (14%)	55 (24%)	88 (19%)	
5+	38 (16%)	30 (13%)	68 (15%)	
Unknown	4 (2%)	1 (0.4%)	5 (1%)	
Number of days ever drank alcohol since birth				
Never	199 (85%)	133 (58%)	332 (72%)	<0.0001
1–2	14 (6%)	40 (17%)	54 (12%)	
3–9	11 (5%)	29 (13%)	40 (9%)	
10–19	2 (1%)	10 (4%)	12 (3%)	
≥20	5 (2%)	13 (6%)	18 (4%)	
Unknown	2 (1%)	4 (2%)	6 (1%)	

*Fisher's exact test for rural versus urban differences.
CFCS, Children and Families Cohort Study.

Table 5 Paediatric cancers diagnosed 1994–2013* among children residing at birth in the CFCS catchment area

Types of paediatric cancers	Number of cases diagnosed 1994–2003	Number of cases diagnosed 2004–2013	Total (%)
Leukaemia	16	34	50 (36.5%)
Acute lymphoblastic leukaemia	13	18	31
Acute myeloid leukaemia	3	13	16
Myelodysplastic syndrome	0	2	2
Other types of leukaemia	0	1	1
Lymphoma	5	4	9 (6.6%)
Hodgkin lymphoma	1	1	2
non-Hodgkin's lymphoma	3	3	6
Other lymphoma	1	0	1
Brain tumours	7	6	13 (9.5%)
Astrocytoma	3	3	6
Medulloblastoma	0	0	0
Primitive neuroectodermal tumour	0	0	0
Other brain tumours	4	3	7
Retinoblastoma	0	0	0
Renal Tumours	8	1	9 (6.6%)
Wilms' tumours	7	1	8
Other renal tumours	1	0	1
Hepatic tumours	3	1	4 (2.9%)
Hepatoblastoma	3	0	3
Other hepatic tumours	0	1	1
Malignant bone tumours	1	2	3 (2.2%)
Osteosarcomas	1	1	2
Other malignant bone tumours	0	1	1
Soft tissue sarcomas	2	1	3 (2.2%)
Rhabdomyosarcoma	2	0	2
Other soft tissue sarcomas	0	1	1
Germ cell tumours	2	10	12 (8.8%)
Testicular cancer	1	0	1
Ovarian tumours	0	4	4
Other germ cell tumours	1	6	7
Carcinomas	1	2	3 (2.2%)
Thyroid cancer	1	2	3
Melanoma	0	0	0
Other types of carcinoma	0	0	0
Unspecified cancers	15	16	31 (22.6%)
Total cancers	60	77	137
Other related conditions			
Aplastic anaemia	12	26	38
Fanconi anaemia	0	1	1

*Diagnosed in eight hospitals.
CFCS, Chinese Children and Families Cohort Study.

We also note significant differences in reported parity and gravidity, consistent with data reported at CIP enrolment in 1993–1995.

The lack of urban–rural differences reported by offspring may reflect adolescent lifestyle changes over time, as illustrated by a recent report on obesity among children in Shandong Province, China.[22] The higher urban compared with rural prevalence of childhood overweight and obesity in Shandong during 1985–2005 no longer existed in 2014 due to the increasing prevalence of overweight and obesity among rural children over time, a change attributed to economic development and lifestyle changes in rural areas.

Strengths and limitations

Compared with many cohort studies, the proportion of families refusing to participate was relatively small, but strategies should be developed to further minimise refusals and entice higher participation. New strategies are needed to locate offspring who are increasingly likely to move away from their childhood residences for educational or employment opportunities. The ideal approach for identifying incident paediatric cancers in the Chinese Children and Families Cohort Study would have been linkage with population-based cancer registries, but there have been no long-standing population-based cancer registries of high quality in the geographic regions where the original CIP was carried out. Although the pilot study included different types of hospitals where children with paediatric cancer might be initially seen and treated, the likely incomplete ascertainment of certain cancer outcomes, a known problem described in compendia of international population-based cancer registry data,[23] suggests the need for learning more about referral patterns for paediatric cancers. Focus groups of hospital and medical professional society leaders would be useful to discuss strategies for improving identification of paediatric cancer cases, particularly those diagnosed in earlier time periods. In the absence of comprehensive coverage of the geographic catchment area by high-quality population-based cancer registries, it is difficult to assess the likely success of matching cohort members with the paediatric cancer cases identified through the hospital component of the pilot study. A more expensive strategy would be to add active follow-up all offspring and parents to identify and verify incident paediatric cancers and to review death certificates to confirm those reported as deceased. In the absence of death certificates, particularly in the early time periods, verbal autopsy interviews may be needed.

Overall, the pilot study revealed positive results for re-identifying, tracing, interviewing and obtaining anthropometric measurements in the original CIP families to establish the new CFCS cohort. A larger feasibility study over a broader geographic region is needed to verify that the strategies used in the current pilot study would continue to yield success in tracing, locating and obtaining the high participation levels needed for cohort follow-up. The large number of paediatric cancers identified is also promising, but further work is needed to improve the level of ascertainment, and test the feasibility of matching paediatric cancers to the CIP children. If a larger feasibility study is successful, we propose to carry out a prospective record linkage CFCS to compare risk of paediatric leukaemia, brain tumours and other paediatric cancers in offspring of 130 142 Chinese mothers who took vs offspring of 117 689 mothers who did not take FA supplements before and during early pregnancy in the 1993–1995 CIP to complement case–control study findings of reduced risks of childhood leukaemia associated with mothers' periconceptional use of FA. In addition, the new CFCS cohort would be a valuable scientific resource that could evaluate a wide range of exposures and outcomes, and address many important research questions once assembled.

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Contributors MSL, LW, RJB, AC, LH, LF, ZL, NP, CMK, XL, JS and YW: study concept and design, oversight of all aspects of the study, reviewed data and wrote manuscript. NW, PY and XS: overall supervision of field work and training, and development of operational field manuals. FM: supervised field work and training of interviewers in rural country. RY: supervised field work and training of interviewers in urban county. NW, LF, PY and BW: conducted quality control supervisory visits and other quality control efforts; JF, RJB, AC, LF, MSL and NP: oversaw data entry, manual and electronic data review, and conducted data analysis. LH, LF, SC, MSL and RJB: responsible for financial supervision. FL, XL, FLv, CM, YT, WW, HW and LZ: provided key assistance with access and collaboration of eight hospitals, developed and reviewed the field manual for identifying eligible paediatric cancer cases, oversaw efforts to identify eligible pediatric cancer cases, oversaw abstracting of medical records, reviewed medical record abstracts and determined final diagnoses of paediatric cancer cases.

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Competing interests None declared.

Ethics approval The protocol was approved by the institutional ethics review committees including: the National Cancer Institute Special Studies Institutional Review Board (NCI SSIRB - 11CN165 for original and annual renewals); the US Centers for Disease Control and Prevention, which relied on the NCI SSIRB original and annual IRB approvals (CDC protocol 6140); and the Chinese Center for Disease Control and Prevention (CCDC protocol 201110 approved August 8, 2011). Informed written consent was obtained for all aspects of data collection (interviews and anthropometric measurements) from all subjects aged ≥18. Written assent was obtained from children under age 18. The participants all received certificates of appreciation; mothers received vouchers for purchasing groceries (US$ value = $15); children received memory sticks (US$ value = $7.60. Identification of pediatric cancers diagnosed during 1994-2013 in the catchment area of the original CIP study was carried out within each hospital and data collected were stripped of all personal identifying information before being provided to the Chinese CDC and other collaborators.

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Data sharing statement The study protocol, data collection instruments, field and coding manuals are available from the corresponding author upon request. If the full-scale study is funded, the findings would be shared with the subjects, public health officials and medical professionals through newsletters and other types of communication. The main results of the study will also be reported in peer-reviewed scientific journals, and at professional society meetings and international conferences. Qualified researchers can also contact the Steering Committee for the study and seek collaboration with study investigators in research projects that would use study data.

REFERENCES

1. Denholm R, De Stavola B, Hipwell JH, *et al*. Pre-natal exposures and breast tissue composition: findings from a British pre-birth cohort of young women and a systematic review. *Breast Cancer Res* 2016;18:102.
2. Potischman N, Troisi R, Vatten L. The life course approach to cancer epidemiology. In: *A life course approach to chronic disease epidemiology*. 2nd edn. New York: Oxford University Press, 2004.
3. Greaves MF, Wiemels J. Origins of chromosome translocations in childhood leukaemia. *Nat Rev Cancer* 2003;3:639–49.
4. Roman E, Lightfoot T, Picton S. Cancers in children. In: Thun MJ, Linet MS, Cerhan JR, Haiman C, Schottenfeld D, eds. *Schottenfeld and Fraumeni Cancer epidemiology and prevention*. 4th edn. New York: Oxford University Press. 2018.
5. Birch JM. Genes and cancer. *Arch Dis Child* 1999;80:1–3.
6. Little MP, Wakeford R, Kendall GM. Updated estimates of the proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionising radiation. *J Radiol Prot* 2009;29:467–82.
7. Bailey HD, Fritschi L, Infante-Rivard C, *et al*. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium. *Int J Cancer* 2014;135:2157–72.
8. Bailey HD, Fritschi L, Metayer C, *et al*. Parental occupational paint exposure and risk of childhood leukemia in the offspring: findings from the Childhood Leukemia International Consortium. *Cancer Causes Control* 2014;25:1351–67.
9. Marcotte EL, Thomopoulos TP, Infante-Rivard C, *et al*. Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC). *Lancet Haematol* 2016;3:e176–e185.
10. Metayer C, Petridou E, Aranguré JM, *et al*. Parental tobacco smoking and acute myeloid leukemia: the childhood leukemia international consortium. *Am J Epidemiol* 2016;184:261–73.
11. Metayer C, Milne E, Dockerty JD, *et al*. Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: a Childhood Leukemia International Consortium study. *Epidemiology* 2014;25:811–22.
12. Rudant J, Lightfoot T, Urayama KY, *et al*. Childhood acute lymphoblastic leukemia and indicators of early immune stimulation: a Childhood Leukemia International Consortium study. *Am J Epidemiol* 2015;181:549–62.
13. Linet MS, Wacholder S, Zahm SH. Interpreting epidemiologic research: lessons from studies of childhood cancer. *Pediatrics* 2003;112:218–32.
14. Schüz J, Spector LG, Ross JA. Bias in studies of parental self-reported occupational exposure and childhood cancer. *Am J Epidemiol* 2003;158:710–6.
15. Hatch EE, Kleinerman RA, Linet MS, *et al*. Do confounding or selection factors of residential wiring codes and magnetic fields distort findings of electromagnetic fields studies? *Epidemiology* 2000;11:189–98.
16. Bunin GR, Spector LG, Olshan AF, *et al*. Secular trends in response rates for controls selected by random digit dialing in childhood cancer studies: a report from the Children's Oncology Group. *Am J Epidemiol* 2007;166:109–16.
17. Hartge P. Participation in population studies. *Epidemiology* 2006;17:252–4.
18. Puumala SE, Spector LG, Robison LL, *et al*. Comparability and representativeness of control groups in a case-control study of infant leukemia: a report from the Children's Oncology Group. *Am J Epidemiol* 2009;170:379–87.
19. Berry RJ, Li Z, Erickson JD, *et al*. Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. *N Engl J Med* 1999;341:1485–90.
20. National Bureau of Statistics of China. Annual Data. [04/16/2017]. http://www.stats.gov.cn/english/Statisticaldata/AnnualData/
21. Liu X, Li N, Liu C, *et al*. Urban-rural disparity in utilization of preventive care services in China. *Medicine* 2016;95:e4783.
22. Zhang YX, Wang ZX, Zhao JS, *et al*. Prevalence of overweight and obesity among children and adolescents in shandong, china: urban-rural disparity. *J Trop Pediatr* 2016;62:293–300.
23. Forman D, Bray F, Brewster DH, *et al*. *Cancer incidence in five continents, Vol. X. IARC scientific publication No. 164*. Lyon: International Agency for Research on Cancer, 2014.