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META-ANALYSIS

Risk for childhood leukemia associated with maternal and paternal age

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Abstract The role of reproductive factors, such as parental age, in the pathogenesis of childhood leukemias is being intensively examined; the results of individual studies are controversial. This meta-analysis aims to quantitatively synthesize the published data on the association between parental age and risk of two major distinct childhood leukemia types in the offspring. Eligible studies were identified and pooled relative risk (RR) estimates were calculated using random-effects models, separately for childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Subgroup analyses were performed by study design, geographical region, adjustment factors; sensitivity analyses and meta-regression analyses were also undertaken. 77 studies (69 case–control and eight cohort) were deemed eligible. Older maternal and paternal age were associated with increased risk for childhood ALL (pooled RR = 1.05, 95 % CI 1.01–1.10; pooled RR = 1.04, 95 % CI 1.00–1.08, per 5 year increments, respectively). The association between maternal age and risk of childhood AML showed a U-shaped pattern, with symmetrically associated increased risk in the oldest (pooled RR = 1.23, 95 % CI 1.06–1.43) and the youngest (pooled RR = 1.23, 95 % CI 1.07–1.40) extremes. Lastly, only younger fathers were at increased risk of having a child with AML (pooled RR = 1.28, 95 % CI 1.04–1.59). In conclusion, maternal and paternal age represents a meaningful risk factor for childhood leukemia, albeit of different effect size by leukemia subtype. Genetic and socio-economic factors may underlie the observed associations. Well-adjusted studies, scheduled by large consortia, are anticipated to satisfactorily address methodological issues, whereas the potential underlying genetic mechanisms should be elucidated by basic research studies.

Keywords Childhood leukemia · Parental age · Meta-analysis · Meta-regression · Risk factor

Introduction

The two most common subtypes of childhood leukemia are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Genetic, environmental and lifestyle risk factors have been addressed in the literature regarding the pathogenesis of these conditions [1], including ionizing radiation [2], chemicals, timing of infectious diseases [3], allergy [4], parental smoking [5], maternal and childhood diet [6, 7], fertility treatments [8, 9] and birth weight [10]. The role of parental reproductive factors in the pathogenesis of childhood cancer seems to represent an intensively examined field, with rapid accumulation of knowledge [11].

The notion of maternal age in reproductive epidemiology becomes increasingly important, on account of the postponement of the first pregnancy to a later age due to the pursuit of career opportunities, as well as the growing

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awareness of infertility treatment options [12]. Parental age may therefore represent a multivalent index, integrating infertility problems, life decisions [13], as well as the socio-economic status of the family in which children are born [14].

Numerous studies examining the association between leukemia risk and parental age (maternal or paternal) have reached controversial results [15–19]. A meta-analysis has been recently published [20], addressing the association between risk for childhood ALL and maternal factors; among the latter, maternal age was not significantly associated with ALL risk. On the contrary, significant associations with birth order, maternal education and maternal smoking were observed [20]. Nevertheless, it should be underlined that the aforementioned meta-analysis suffered from methodological problems [21] and treated maternal age as a binary variable (>30 vs. <30 years or >35 vs. <35 years), precluding any examination of an underlying U-shaped curve; of note, the effect of paternal age was not addressed. Meaningful subgroups, such as separate synthesis in cohort and case–control studies, were not addressed either therein. Moreover, the association between parental age and childhood AML represents a totally undiscovered field at the meta-analytical level.

Taking the aforementioned into account, the present meta-analysis aims to examine the associations between parental age (maternal as well as paternal) with childhood leukemia types (ALL, AML), addressing a variety of potentially meaningful methodological considerations in the individual studies.

Materials and methods

Search strategy and eligibility of studies

This meta-analysis was performed in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. The potentially eligible publications were sought in PubMed using the search algorithm [(-parental OR paternal OR maternal OR mother OR mother's OR father OR father's) AND age] AND (leukemia OR leukaemia OR leukemias OR leukaemias OR [(haematological OR hematological) AND (cancer OR cancers OR malignancy OR malignancies)] AND (child OR children OR childhood) with end of search date September 30, 2014. There was no restriction regarding publication language; reference lists were systematically searched for relevant articles ("snowball" procedure).

Eligible articles included case–control as well as cohort studies examining the association between maternal/paternal age and risk of childhood leukemia (acute lymphoblastic leukemia, ALL; acute myeloid leukemia, AML; mixed reporting of leukemia cases) in the offspring. Studies exclusively recruiting children with Down syndrome, or studies whose controls were not cancer-free children were not deemed eligible for this meta-analysis. Similarly to previous meta-analyses issued by our team [5, 14], the most recent NARECHEM data were provided updating earlier relevant publications on the field.

In case of overlapping study populations (>50 % of cases), only the larger study was included. Nevertheless, in cases of partial overlap (25–50 %), as was the case in large consortia, both studies were retained and one of them was thereafter removed in a sensitivity analysis. The corresponding authors were contacted twice (a reminder e-mail was sent 7 days after the first e-mail) for the clarification of overlap between studies in case this was not clear from the manuscripts. The selection of studies was performed by authors working in pairs, blindly to each other; in case of disagreement, the decision was made with team consensus.

Data extraction and effect estimates

The extraction of data comprised first author's name, study year, journal, type of study, follow-up period, study region, subjects' age (range, mean), percentage of males, numbers and sources of information for cases and controls (for case–control studies), matching factors (for case–control studies), cohort size, incident cases, cohort features and definition of the outcome (for cohort studies), type of cases (incident; mortality), case ascertainment, participation rate, source of information regarding parental age, factors adjusted for in multivariate analyses, primary exposure of interest in the studies. The data abstraction was performed by authors working in pairs, blindly to each other; in case of disagreement, the decision was made with team consensus.

The maximally adjusted effect estimates i.e., Odds Ratios (ORs) for case–control studies or Relative Risks (RRs) for cohort studies, with their Confidence Intervals (CIs) were extracted from each study by leukemia subtype, maternal or paternal age categories or increments. In case the aforementioned information was not available, crude effect estimates and 95 % CIs were calculated by means of 2×2 tables presented in the articles.

Statistical analysis

Random-effects (DerSimonian-Laird) models were used to calculate pooled effect estimates, as appropriate. Between-study heterogeneity was evaluated through Cochran Q statistic and by estimating I^2 [22]. Pooling of studies comprised two distinct approaches: first, the incremental effect estimates of maternal/paternal age (in 5-year increments) on childhood leukemia risk were pooled. Moreover, the "youngest" versus intermediate, as well as the "oldest"

versus intermediate comparisons between age categories were pooled, to evaluate the presence of U-shaped effects, if any. Sensitivity analyses were performed by partial overlap and cut-off values of extreme age categories (>35, >40, <20 years of age).

Separate analyses were conducted for ALL, AML and studies with mixed reporting of leukemia cases; maternal and paternal age was analyzed separately. Subgroup analyses were performed by study design (case–control; cohort), geographical region and quality of studies (degree of adjustment; overall Newcastle-Ottawa Quality score). Regarding the degree of adjustment, the term "with mutual adjustment" refers to studies that have adjusted maternal age for paternal age measurements, and paternal for maternal, whereas the term "no mutual adjustment" refers to studies that adjusted only for other factors. Statistical analysis was performed using STATA/SE version 13 (Stata Corp, College Station, TX, USA).

Risk of bias, meta-regression analysis

The quality of the included studies was evaluated using the Newcastle-Ottawa Quality scale [23]. Regarding longitudinal cohort studies, the item assessing whether the follow-up period was enough for the outcome to occur, the cut-off value was a priori set at 4 years, whereas the item evaluating the adequacy of follow-up required a minimum of 80 %. The evaluation of the quality in the eligible studies was performed by authors working in pairs, blindly to each other; in case of disagreement, the decision was made with team consensus.

Egger's statistical test was implemented to evaluate the evidence of publication bias. For the interpretation of Egger's test, statistical significance was defined as $p < 0.1$. Meta-regression analysis aimed to assess whether publication year (in increments of 10 years, assuming there is a continuous change in effect estimates over calendar time), gender of the offspring (expressed as percentage of males in the eligible studies/study arms) and age (expressed as the mean age in the individual studies/study arms) modified the documented associations. Meta-regression analysis and evaluation of publication bias were performed using STATA/SE 13 (Stata Corp, College Station, TX, USA).

Results

The flow chart describing the successive steps during the selection of eligible studies is presented in Supplemental Figure 1. A total of 767 abstracts were identified and screened; details regarding the selection of studies, the e-mails sent to the corresponding authors and the reference list of the included studies are presented in Supplemental Results, whereas Supplemental Table 1 presents the list of studies retrieved in full text that were afterwards excluded for a variety of stated reasons.

Tables 1 and 2 present the characteristics of the included studies, namely 69 case–control and eight cohort studies, respectively. Taken as a whole, 67 studies reported on maternal age as a categorical variable, namely 60 case–control studies (corresponding to 25,335 ALL cases, 4164 AML cases, 24,469 cases of "mixed" childhood leukemias and 111,055 controls) and seven cohort studies (1850 incident ALL, 114 AML and 1746 mixed leukemia cases in a total cohort size of 12,522,500 children). On the other hand, 15 studies examined maternal age as an incremental variable, namely 12 case–control studies (corresponding to 13,642 ALL, 2461 AML, 14,068 "mixed" childhood leukemia cases and 56,061 controls) and three cohort studies (1003 incident ALL, 114 AML and 1427 mixed leukemia cases in a total cohort size of 8,608,739 children).

Regarding paternal age, 38 studies examined paternal age as a categorical variable, namely 34 case–control studies (corresponding to 21,371 ALL cases, 3647 AML cases, 15,688 cases of "mixed" childhood leukemia cases and 69,740 controls) and four cohort studies (1191 incident ALL, 114 AML and 1427 mixed leukemia cases in a total cohort size of 9,043,672 children). Twelve studies evaluated paternal age as an incremental variable, namely nine case–control studies (corresponding to 12,736 ALL, 2202 AML, 13,522 "mixed" childhood leukemia cases and 46,674 controls) and three cohort studies (1003 incident ALL, 114 AML and 1427 mixed leukemia cases in a total cohort size of 8,608,739 children).

Maternal age and risk for ALL

The upper part of Table 3 presents the results of meta-analyses regarding the association between maternal age and risk of ALL. The incremental analysis pointed to an association between older maternal age and increased risk for childhood ALL (pooled RR = 1.05, 95 % CI 1.01–1.10, per 5 years, Fig. 1), which was particularly evident among cohort and European studies. Of note, this association was also significant among the subset of unadjusted studies (pooled RR = 1.09, 95 % CI 1.03–1.14, Supplemental Figure 2).

Similarly to this pattern, the "oldest versus middle" comparison pointed to increased risk for ALL among the offspring from oldest mothers (pooled RR = 1.10, 95 % CI 1.00–1.21, Supplemental Figures 3–6), a finding which

Table 1 Characteristics of the 69 eligible case–control studies

Author (year)	Cases (N)	Controls (N)	Study period	Region	Males (%)	Mean age (years)	Age range (years)	Definition/features of cases–exclusion criteria	Type of cases	Case ascertainment
Ager (1965)	103 LEUK	103	1953–1957	Minnesota, USA	52.68[a]	2.91[a]	0–4	Minnesota residents aged 0–4 years who died of leukemia; Down's syndrome excluded	Mortality	Death certificates and medical records
Ajrouche (2014)	747 LEUK (636 ALL; 100 AML; 11 other)	1421	2010–2011	France	54.98	5.91	<15	LEUK patients identified from the Registries of the pediatric oncology units; excluded: adopted, biological mother had died, was absent, did not speak French, had a serious social problem or psychiatric disorder, could not be interviewed for ethical reasons because the child was in palliative care or had died	Incident	Registry-based
Castro-Jimenez (2011)	85 ALL	85	2000–2005	Bogotá, Bucaramanga, Colombia	NR	NR	<15	Newly diagnosed, histologically and clinically confirmed ALL patients, identified through the review of institutional registries; excluded: Down's syndrome, adopted, living with people other than the biological parents	Incident	Registry-based
CLIC-ADELE (2014)	240 ALL; 36 AML	288	1993–1999	France	58.69	5.43	0–14	Newly diagnosed, primary LEUK patients residing in the hospital catchment area, and in complete remission or in good condition	Incident	Hospital-based
CLIC-ESCALE (2014)	648 ALL; 101 AML	1681	2003–2004	France	54.94	5.51	0–14	Newly diagnosed LEUK patients, residing in France at the time of diagnosis, identified from nationwide, population-based, cancer registry; excluded; adopted, biological mother had died, did not speak French, presented with a psychiatric disorder or could not be interviewed for ethical reasons because the child was in palliative care or had died	Incident	Registry-based
CLIC-GCCR (2014)	751 ALL; 130 AML	2458	1988–1994	Germany	57.26	5.31	0–14	LEUK patients, identified from nationwide, population-based cancer registry	Incident	Registry-based
CLIC-NARECHEM 93–94 (2014)	140 ALL; 13 AML	300	1993–1994	Greece	55.85	6.06	0–14	Bone marrow confirmed, incident LEUK patients, identified through a nationwide network of childhood hematologists/oncologists; non-Greek nationality excluded	Incident	Registry-based
CLIC-NZCCS (2014)	97 ALL; 22 AML	303	1990–1993	New Zealand	53.55	5.59	0–14	Newly diagnosed, histologically and hematologically confirmed LEUK patients, born and resident in New Zealand, identified through nationwide registry; adopted excluded	Incident	Hospital-based
CLIC-Quebec (2014)	790 ALL	790	1980–2000	Quebec, Canada	57.91	4.41	0–14	ALL patients recruited from province-wide covering hospitals; clinical diagnosis by oncologist or hematologist; excluded: adopted, living in foster families, residence out of Canada, parents spoke neither French nor English or were both unavailable for interview	Incident	Hospital-based
CLIC-SETIL (2014)	32 AML	1044	1998–2001	Italy	53.62	4.47	0–14	Newly diagnosed LEUK patients, identified through nationwide clinical database	Incident	Registry-based
CLIC-UKCCS (2014)	1461 ALL; 248 AML	3448	1991–1996	UK	55.96	4.97	0–14	LEUK patients, identified through population-based tailored referral systems; residence in England, Scotland or Wales	Incident	Registry-based

Table 1 continued

Author (year)	Cases (N)	Controls (N)	Study period	Region	Males (%)	Mean age (years)	Age range (years)	Definition/features of cases–exclusion criteria	Type of cases	Case ascertainment
Ding (2012)	176 ALL	180	2010–2011	Shanghai, China	54.20	5.79	0–14	Newly diagnosed hospital ALL patients; excluded: adopted, lacking urinary samples or important questionnaire data, history of cancer, residence out of Shanghai	Incident	Hospital-based
Dockerty (1999)	121 LEUK (97 ALL)	303	1990–1993	New Zealand	NR	NR	0–14	Newly diagnosed LEUK patients, identified through nationwide population-based cancer registry and the public hospital admission/discharge computer system; born and resident in New Zealand; adopted excluded	Incident	Registry-based
Dockerty (2001)	3153 ALL; 563 ANLL	3878	1968–1980 1982–1986	England and Wales, UK	NR	NR	0–14	LEUK patients identified through nationwide population-based registry; excluded: adopted, born outside of marriage or in 1981	Incident	Registry-based
Farioli (2014)	557 ALL	855	1998–2003	Italy	54.25	4.20	0–10	Incident ALL cases, identified through nationwide population-based registry; second primary neoplasms excluded	Incident	Registry-based
Feller (2010)	425 ALL	3350	1991–2006	Switzerland	58.57	6.34	0–14	ALL patients, identified through linkage of national cancer registry census records; residence in Switzerland at the time of diagnosis	Incident	Registry-based
Ferreira (2013)	252 LEUK	423	1999–2007	Brazil	52.74	NR	<2	Morphologically, immunophenotypically and cytogenetically-confirmed ALL and AML hospital patients; excluded: congenital syndromes, myelodysplasia, adoptive parents, or unknown biological mothers not eligible to be enrolled	Incident	Hospital-based
Ford (1959)	78 LEUK	306	1951–1955	Louisiana, USA	58.85	4.40	<10	Leukemia deaths obtained through review of death certificates	Mortality	Death certificates
Gao (2014)	105 LEUK	105	2008–2011	Shanghai, China	45.00	5.80	<15	Newly diagnosed hospital-admitted LEUK patients; excluded: diagnostic criteria not fulfilled, adopted, refusal of participation, uncompleted questionnaire	Incident	Hospital-based
Gholami (2013)	130 LEUK	260	2003–2009	West Azerbaijan, Islamic Republic of Iran	55.38	6.18	<15	LEUK patients, residing in West Azerbaijan province at the time of diagnosis	Incident	Registry-based
Graham (1966)	319 LEUK	884	1959–1962	Urban population centers and surrounding rural counties, NY State (big cities excluded: NY, Baltimore, Minneapolis-St. Paul), USA	51.83	7.29	0–15	LEUK patients identified through cancer registry and medical records	Incident	Registry-based
Hairul (2008)	128 LEUK	128	2001–2007	Klang Valley, Malaysia	55.08	5.03	<15	Histologically confirmed LEUK	Incident	Hospital-based
Hassanzadeh (2011)	163 LEUK	163	2005–2009	Fars province, Southern Iran	61.30	7.74	<18	Hospital-derived, bone marrow and flowcytometry-confirmed LEUK patients	Incident	Hospital-based

Table 1 continued

Author (year)	Cases (N)	Controls (N)	Study period	Region	Males (%)	Mean age (years)	Age range (years)	Definition/features of cases–exclusion criteria	Type of cases	Case ascertainment
Hernadez-Morales (2009)	47 LEUK	47	2007–2008	Baja California, Mexico	61.70	7.20	NR	Hospital-derived, incident, bone marrow-confirmed LEUK patients	Incident	Hospital-based
Johnson (2008)	559 ALL; 87 AML	8750	1974–2004	Minnesota, USA	51.94	NR	28 days-14	LEUK patients identified through linkage of Minnesota Cancer Surveillance System to birth records; excluded: subjects who died during the neonatal period, were born in 1980 or later, Down's syndrome (with some exceptions), previous lymphoma	Incident	Registry-based
Johnson (2009)	5561 LEUK	NR	1970–2004	California, Minnesota, Texas, Washington, NY (NY City excluded), USA	NR	NR	0–14	Linkage of state's cancer registry to birth certificates; excluded: younger than 28 days of age, Down's syndrome	Incident	Registry-based
Johnson (2010)	443 LEUK	324	1996–2006	USA, Canada	NR	NR	<1	ALL and AML patients retrieved from nationwide cancer database. Excluded; Down's syndrome, mother did not speak English or Spanish, biological mother not available for a telephone interview	Incident	Hospital-based
Jourdan-Da Silva (2004)	408 ALL; 65 AML	567	1995–1998	France	56.35[a]	5.70[a]	<15	Population-based, nationwide cancer registry incident AL patients, resident in mainland France at the time of diagnosis, whose was able to fill out a questionnaire and the doctor authorized contact with the mother. Excluded were cases in four regions that were already involved in a previous hospital-based case–control study, and the cases in four other regions in which the oncology department could not contribute to the study for practical reasons; Down's syndrome	Incident	Hospital-based
Kamper-Jogensen (2008)	559 ALL	5590	1989–2004	Denmark	55.99	5.77	0–15	Incident ALL patients retrieved from Scandinavian cancer registries. Excluded: Down's syndrome	Incident	Registry-based
Kaye (1991)	337 ALL	1336	1969–1988	Minnesota, Wisconsin, N. Dakota, USA	52.00	4.70	<18	ALL patients identified through linkage of pediatric oncology records to birth certificates and supplemental information forms	Incident	Hospital-based
Knox (1983)	1321 LEUK	1321	1953–1979	England, UK	NR	NR	NR	LEUK patients retrieved from records of The Oxford Survey of Childhood Cancer	Mortality	Registry-based
Kumar (2014)	132 LEUK	132	2008–2012	Rohtak, India	69.70	10.89	<18	LEUK patients diagnosed at Pharma University of Health Sciences	Incident	Hospital-based
Larfors (2012)	2199 ALL; 461 AML	10,640	1962–2008	Sweden	51.02	NR	<15	ALL, AML patients retrieved from 5 nationwide registries; APL excluded	Incident	Registry-based
Laval (1988)	200 LEUK	200	1977–1982	Lyon, France	NR	NR	<15	LEUK patients	Incident	Hospital-based
MacArthur (2008)	399 LEUK	399	1990–1995	Five provinces of Canada	50.90	5.28	<15	Incident cases of LEUK, identified through pediatric oncology treatment centers and population-based cancer registries; Down's syndrome excluded	Incident	Registry-based

Table 1 continued

Author (year)	Cases (N)	Controls (N)	Study period	Region	Males (%)	Mean age (years)	Age range (years)	Definition/features of cases–exclusion criteria	Type of cases	Case ascertainment
Manning (1957)	187 LEUK	44	1953–1956	Boston, Massachusetts, USA	NR	NR	0–14	Histologically confirmed LEUK patients at the Children's Cancer Research Foundation in Boston, Massachusetts	Incident	Registry-based
McLaughlin (1993)	112 LEUK	890	1950–1988	Ontario, Canada	51.70	3.96	0–14	LEUK deaths (1950–1963) or incident (1964–1988) cases, retrieved from Ontario Cancer Registry and birth certificates, born to mothers who lived near an operating nuclear facility in Ontario at the time of the child's birth; diagnosis confirmed by pathology reports or other hospital/clinic records	Incident and mortality	Registry-based
Mertens (1998)	2117 ALL; 605 AML	3137	1983–1994	USA, Canada, Western Australia	53.30	5.61	<18	ALL, AML patients; diagnosis confirmed at a Childhood Cancer Group institution; presence of a telephone in the family household at the time of diagnosis; physician's permission to contact the case patient's parents; biologic mother of the case patient available, able to speak English, and consenting to be interviewed	Incident	Registry-based
Milne (2010)	393 ALL	1249	2003–2007	Australia	53.41	5.47	<15	ALL patients identified through all pediatric oncology centers in Australia; initial remission was achieved; biological mother available, with adequate English skills	Incident	Registry-based
Milne (2012)	388 ALL	868	2003–2007	Australia	46.50	5.37	<15	ALL patients identified through all pediatric oncology centers in Australia	Incident	Registry-based
Monge (2007)	300 LEUK	579	1995–2000	Costa Rica	51.42	NR	0–14	LEUK cases identified through population-based, nationwide cancer registry and confirmed from hospital records	Incident	Registry-based
NARECHEM (1996–2013)	1246 LEUK (1099 ALL; 131 AML)	1246	1996–2013	Greece	56.30	5.90	0–14	Incident hematologically and histologically confirmed ALL, AML cases in six Pediatric Hematology-Oncology Departments across Greece and registered in the Nationwide Registry for Childhood Hematological Malignancies (NARECHEM)	Incident	Registry-based
Oksuzyan (2012)	5788 (4721 ALL; 852 AML; 215 Other)	5788	1988–2008	California	55.80	4.74	<16	LEUK cases identified through statewide population-based cancer registry	Incident	Registry-based
Pedersen (2014)	879 LEUK	1621	1968–1991	Denmark	NR	NR	<15	LEUK cases identified through nationwide Danish Cancer Registry; excluded: previous cancer diagnosis	Incident	Registry-based
Perez-Salvidar (2008)	193 LEUK	193	1999–2000	Mexico City, Mexico	58.29	NR	<16	Histologically confirmed LEUK cases, identified through four hospitals in Mexico City	Incident	Hospital-based
Perillat (2001)	279 LEUK	285	1995–1999	Lille, Lyon, Nancy, Paris, France	58.87	5.57	0–15	Newly diagnosed, incident, primary LEUK cases recruited from 4 hospitals in France; residence in the hospital catchment area; complete remission or good condition	Incident	Hospital-based
Petridou (1997a)	117 LEUK	202	1993–1994	Greece	NR	NR	0–14	Bone-marrow confirmed leukemia cases diagnosed through a nation-wide network of childhood hematologists- oncologists among Greek nationals	Incident	Registry-based
Petridou (1997b)	153 LEUK	300	1993–1994	Greece	55.85	6.17	0–14	Bone marrow-confirmed, incident LEUK cases diagnosed through a nationwide network of childhood hematologists/oncologists among Greek nationals	Incident	Registry-based

Table 1 continued

Author (year)	Cases (N)	Controls (N)	Study period	Region	Males (%)	Mean age (years)	Age range (years)	Definition/features of cases–exclusion criteria	Type of cases	Case ascertainment
Petridou, Swedish arm (2012)	520 LEUK	5200	1995–2007	Sweden	51.15	3.45	0–12	Population-based, nationwide identification of leukemia cases through linkage of the Swedish Birth to Cancer Registry	Incident	Registry-based
Podvin (2006)	376 ALL; 85 AML	4980	1981–2003	Washington State, USA	NR	NR	<20	LEUK patients identified through linkage of Washington State birth certificate and cancer registry	Incident	Registry-based
Puumala (2010)	443 LEUK (264 ALL; 172 AML)	324	1996–2002, 2003–2006	USA, Canada	48.76	NR	<1	Confirmed ALL, AML cases collected in two phases; children who died before the study period were included; treated or diagnosed at a participating institution in the USA or Canada; biological mother spoke English or Spanish (phase II), and was available by telephone; Down's syndrome excluded	Incident	Registry-based
Roman (2005)	1254 LEUK (179 AML)	4864	1992–1996	UK	55.31	4.38	0–14	LEUK patients identified though nationwide, population-based treatment trials; information about cases not enrolled in trials was obtained from the UKCCSG, the NRCT, or the individual consultant treating the child	Incident	Registry-based
Roman UK arm (2013)	1405 ALL	7463	1991–1996	UK	56.19	5.65	<15	ALL patients born in the UK, without prior malignancy, not living in local authority care	Incident	Registry-based
Roman German arm (2013)	742 ALL	2412	1992–1994	Germany	57.20	5.31	<15	ALL patients identified through the German Childhood Cancer Registry; living in West Germany	Incident	Registry-based
Rubin (2007)	14 LEUK	55	1997–2002	Churchill County, Nevada, USA	50.72	NR	2–20	LEUK patients identified through the Nevada State Health Division	Incident	Registry-based
Rudant (2012)	648 ALL	1681	2003–2004	France	55.00	5.53	<15	ALL patients identified through nationwide cancer registry, resident in France at the time of diagnosis; excluded: adopted, biological mother had died, non-French-speaking, had serious psychiatric disorder, could not be interviewed for ethical reasons	Incident	Registry-based
Rudant (2010)	102 AML	1681	2003–2004	France	55.36	5.56	0–14	AML patients identified through nationwide cancer registry, resident in France at the time of diagnosis; excluded: chromosomal abnormalities, child's death, hospital palliative care, biologic mother dead, non-French-speaking, had serious psychiatric disorder	Incident	Registry-based
Salonen (1975)	373 LEUK	373	1959–1968	Finland	NR	NR	<15	LEUK patients; information collected from nationwide cancer registry, records of Maternity Welfare Centers, and questionnaire sent to the maternity hospitals	Incident	Registry-based
Schlehofer (1996)	121 LEUK	197	1990–1991	West Germany	57.55	5.92	0.5–15	LEUK patients reported to the Childhood Cancer Registry by the respective clinics; residence in Germany; German-speaking parents	Incident	Registry-based
Schuz (1999)	1184 LEUK	2588	1980–1997	Germany	58.35	5.07	0–15	NW: LEUK patients identified from nationwide cancer registry, residing in West Germany at the date of diagnosis NI: LEUK patients identified through embedded ecological study investigating childhood malignancies in the vicinity of German nuclear installations, residing at most 15 km away from a nuclear installation	Incident	Registry-based

Table 1 continued

Author (year)	Cases (N)	Controls (N)	Study period	Region	Males (%)	Mean age (years)	Age range (years)	Definition/features of cases–exclusion criteria	Type of cases	Case ascertainment
Shu (1988)	309 LEUK (172 ALL; 94 ANLL; 43 Other)	618	1974–1986	Shanghai, China	54.00	6.37	<15	Bone marrow (96 %) or peripheral blood smear confirmed LEUK patients, identified from the population-based cancer registry; medical data abstracted from hospital records; adopted excluded	Incident	Registry-based
Shu (1994)	166 LEUK	166	1986–1991	Shanghai, China	63.00	5.10	<15	LEUK patients identified from population-based cancer registry; histopathological data abstracted from hospital records; excluded: refusal to participate; adopted; living with guardians other than natural parents	Incident	Registry-based
Sprehe (2010)	913 LEUK (727 ALL; 124 AML)	13,331	1995–2003	Texas, USA	51.65	NR	<5	LEUK patients identified from population-based, statewide cancer registry linked to birth certificate data; excluded: multiple births, gestational age missing or implausible	Incident	Registry-based
Thompson (2001)	83 ALL	166	1984–1992	Western Australia	61.45	4.87	0–14	ALL patients treated at the referral hospital oncology unit in Western Australia; excluded: T cell and mature B-cell disease, residence in a remote region, parents spoke little English, inappropriate interview due to unexpected child death, the family left the state immediately after diagnosis, diagnosis in the closing weeks of the study so that no controls could be selected	Incident	Hospital-based
Untario (1972)	61 LEUK (18 ALL; 43 AML)	600	1958–1970	Surabaja, Indonesia	NR	NR	<15	LEUK patients retrieved from one hospital; excluded: either maternal age or birth order not mentioned in the case histories available	Incident	Hospital-based
van Duijn, ANLL arm (1994)	80 ANLL	240	1973–1980	NL	58.75	6.31	0–14	ANLL patients identified from the national morbidity registration of the Dutch Childhood Leukemia Study Group	Incident	Registry-based
van Steensel-Moll (1985)	517 ALL	509	1973–1980	Netherlands	NR	NR	<15	Bone marrow-confirmed ALL patients identified from nationwide morbidity register; ethnically foreign children excluded	Incident	Registry-based
Wen (1998)	302 LEUK	558	1983–1988	USA Canada	52.89	NR	0–1.5	Newly-diagnosed LEUK patients, identified through the registration files of a cooperative clinical trials; residence in USA or Canada; existence of a telephone in the patient's residence; biological mother available for interview, English-speaking	Incident	Registry-based
Wong (2006)	278 ALL; 71 ANLL	585	1976–1987	New Zealand	NR	NR	0–14	ALL, ANLL patients identified through linkage of nationwide cancer registry to birth records; excluded: born outside New Zealand, adopted, birth records unavailable or incomplete	Incident	Registry-based

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
Ager (1965)	One sibling and one neighbor for each case; Down's syndrome excluded	Neighborhood, siblings	Cases: 89 %, Controls: NR	Yes	Questionnaire-based interview with the mother, by the senior author or one of several medical students in his clinical years at the University of Minnesota	Maternal age	1:2 on birth date, gender, residence	None	Radiation and chemicals, allergies, infectious diseases, congenital anomalies, pica, trauma, metabolic disturbances, developmental abnormalities, and use of medications
Ajrouche (2014)	No history of cancer; selected using a quota sampling method; excluded: adopted, the biological mother had died or did not speak French	Population	Cases: 93 %, Controls: 86 %	No	Structured questionnaire-based, computer-assisted telephone interview with the mother by trained interviewers	Maternal age	Frequency matching on age, gender	Age, gender	Maternal reproductive history, fertility treatments and folic acid supplementation
Castro-Jimenez (2011)	Neighborhood-based healthy children chosen from a house-to-house search; excluded: Down's syndrome, history of cancer, adopted, living with people other than the biological parents	Hospital and community	Cases: 94 %, Controls: NR	Yes	Structured questionnaire-based in-person interview by non-medical interviewers and field coordinators, blinded on study hypothesis/methods	Maternal, paternal age	Individual 1:1 matching on age, gender	Maternal age: parental exposure to hydrocarbons, parental smoking, maternal SES; paternal age: none	Birth weight
CLIC-ADELE (2014)	Hospitalized mainly in orthopedic departments of the same hospital and residing at the same area as the cases; excluded: history of cancer, birth defect, adopted, incomplete questionnaire	Hospital	Cases: 95 %, Controls: 99 %	NR	Questionnaire-based in-person interview with the mother by medical interviewers	Paternal age	Frequency 1:1 matching on age, gender, hospital, ethnicity	None	Parental occupational pesticide exposure
CLIC-ESCALE (2014)	Population-based, nationwide quotas by age, sex, region; excluded: same as for cases	Population (regional)	Cases: 91 %, Controls: 71 %	NR	Structured questionnaire-based telephone interview with the mother by same for cases and controls trained interviewers	Paternal age	Frequency matching on age, gender	None	Parental occupational pesticide exposure

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
CLIC-GCCR (2014)	Population-based registry (community-based but complete nationwide coverage)	Population	Cases: 82 %, Controls: 71 %	No	Mailed structured questionnaire completed by both parents, if possible; telephone interview validation by trained interviewers	Maternal, paternal age	Age, gender, control region	None	Parental occupational pesticide exposure
CLIC-NARECHEM 93–94 (2014)	Hospitalized for acute conditions, at the same time as the corresponding cases	Hospital	Cases: 100 %, Controls: 96 %	NR	Questionnaire-based interview with the mother	Maternal, paternal age	Individual 1:2 matching on age, gender, residence	None	Parental occupational pesticide exposure
CLIC-NZCCS (2014)	Random selection from nationwide birth registry, residing in New Zealand; adopted excluded	Population (Birth registry)	Cases: 86 %, Controls: 68 %	NR	Structured questionnaire-based interview with the mother; both parents and interviewers blinded to study hypothesis	Maternal, paternal age	Age, gender	None	Parental occupational pesticide exposure
CLIC-Quebec (2014)	Health Insurance file province-wide, population-based registry; excluded: as for cases	Population	Cases: 93 %, Controls: 86 %	NR	Structured questionnaire-based telephone interview with the parents by trained interviewers	Maternal, paternal age	1:1 on age, gender	None	Parental occupational pesticide exposure
CLIC-SETIL (2014)	Randomly selected from the population-based National Health Service Registry	Population	Cases: 91 %, Controls: 69 %	NR	Structured questionnaire-based in-person interview with the parents by trained interviewers	Paternal age	1:2 on date of birth, gender, residence	None	Parental occupational pesticide exposure
CLIC-UKCCS (2014)	Randomly selected from nationwide general practitioner registries	Population	Cases: 93 %, Controls: 64 %	No	In-person (telephone if in-person not possible) interview with the parents or guardian(s) by trained interviewers, using separate but similar structured questionnaires	Paternal age	1:2 on date of birth, gender, residence	None	Parental occupational pesticide exposure
Ding (2012)	Hospital-derived, generally in good health; excluded: as for cases	Hospital	Cases: 83 % Controls: 77 %	NR	Structured questionnaire-based in-person interview with the mother by trained interviewers	Maternal, paternal age	Age, gender, hospital	None	Pyrethroid pesticide exposure
Dockerty (1999)	Randomly selected from nationwide birth records; adopted excluded	Population (regional)	Cases: 92 %, Controls: 69 %	NR	Standardized questionnaire-based in-person interview with the mother; both mothers and interviewers blinded for study hypothesis	Maternal age	Age, gender	Age, gender	Infections and vaccinations

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
Dockerty (2001)	Randomly selected from nationwide birth records; excluded: born outside of marriage or in 1981	Population (district)	Cases: 78 %, Controls: 80 %	Yes	Retrieved from birth records	Maternal, paternal age	1:1 on date of birth, gender, birth registration sub-district	Deprivation score, parity	Parental age
Farioli (2014)	Randomly selected from population registries of the relevant local health authorities	Population (regional)	Cases: 92 %, Controls: 68 %	NR	Standardized questionnaire-based in-person interview with the parents; interviewers not blinded to the case–control status	Maternal, paternal age	Individual 1:2 matching on date of birth, gender, residence	None	Parental smoking
Feller (2010)	Up to 1:8 matched controls randomly selected from the census records	Population	Cases 59 %. Controls: NR	NR	Census records	Maternal, paternal age	Year of birth, gender	None	Family characteristics, including parental age
Ferreira (2013)	Hospitalized for various nonmalignant conditions at the centers where the cases were recruited or at general hospitals in the same cities; excluded: congenital syndromes, myelodysplasia, adoptive parents, or unknown biological mothers were not eligible to be enrolled, cancer diagnosis	Hospital	Cases: 96 %, Controls: 95 %	NR	Standardized questionnaire-based in-person interview with the mother by instructed health staff members, same for cases and controls	Maternal age	Age, geographic area	None	In utero pesticide exposure
Ford (1959)	Death from other than LEUK causes during the same period as cases; excluded: foreign birth, midwife delivery, adopted	Population	Cases 67 %, Controls 50 %	No	Information obtained from the doctors	Maternal age	Age, gender, race, place of death	None	Fetal exposure to diagnostic X-rays
Gao (2014)	Healthy children receiving physical check-up from the department of children's healthcare or who visited the clinic of developmental pediatrics or orthopedics for reasons other than blood diseases and malignant tumors, at the same hospital, and residing in the same home as cases; adopted excluded	Hospital	Cases: 89 % Controls: 61 %	NR	Structured questionnaire-based in person interview with the mother by trained interviewers	Maternal, paternal age	1:1 on age, gender	None	Indoor air pollution
Gholami (2013)	Children free from LEUK or other blood disease, residing in West Azerbaijan province; one hospital and one community (routine health care at health centers) derived control for each case	Hospital and community	Cases: 94 %, Controls: NR	NR	Questionnaire completion using data files and in-person interview with the mother	Maternal, paternal age	1:2 on age, gender	None	Birth weight

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
Graham (1966)	Random stratified selection of households	Neighborhood	Cases: 84 % Controls: 94 %	NR	Questionnaire-based interview of the mother by nurse interviewers blinded as to case–control status	Maternal age	None	None	Preconception, intrauterine and perinatal irradiation
Hairul (2008)	Cancer-free children from the same hospitals as cases, receiving treatment for acute disease other than cancer; excluded if refused to participate	Hospital	NR	No	Structured questionnaire-based in-person interview with the parents or guardians by the researcher or trained research assistants	Maternal, paternal age	None	Family income, paternal social contact, number of elder siblings, family history of cancer, paternal smoking, distance to main road, distance to power line, mutual adjustment for paternal and maternal age	Multiple primary exposures including parental age
Hassanzadeh (2011)	Random sampling	Population	NR	NR	Interview with one of the parents	Maternal age	Individual 1:1 matching on age, gender, residence	Maternal age <20 years: paternal education, maternal education, paternal occupation; Other: none	Maternal and birth characteristics, environmental exposures
Hernadez-Morales (2009)	Randomly selected cancer-free children hospitalized for acute, nonmalignant conditions	Hospital	NR	NR	Questionnaire-based, in-person interview with mother	Maternal age	1:2 on age, gender, residence	None	Multiple primary exposures including maternal age
Johnson (2008)	Randomly selected from birth records; excluded: subjects who died during the neonatal period, were born in 1980 or later	Population	Cases: 84 %, Controls: NR	Yes, with some exceptions	Birth certificates	Maternal age	Birth year	ALL: maternal ethnicity/education, last live birth interval, child gender, birth weight percentile, one minute Apgar score, gestational age, birth year AML: none	Parental and infant characteristics, including maternal age
Johnson (2009)	Randomly selected from state's birth registry; excluded: cases selected as controls	Population (Birth registry)	Cases: 95 %, Controls: NR	Yes (except for Texas before 1984 and Washington before 1989)	Birth records	Maternal, paternal age	1:1 to 1:10 on age, sex	5 year increase and <20 years of maternal and paternal age: maternal race, gender, birth weight, gestational age, birth order, birth year category, plurality, state, mutual (and unmutual) adjustment for maternal and paternal age Other: none	Parental age
Johnson (2010)	Selection through random digit dialing, or. state birth registries	Population (random digit dialing, birth registry)	Cases: 59 %, Controls: 57 %	Yes	Structured telephone interview	Maternal age	Birth year, residence	None	Congenital abnormalities

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
Jourdan-Da Silva (2004)	Randomly selected, matched population controls. Excluded if Down's syndrome	Population	Cases: 60 %, Controls 71 %	Yes	Standardized self-administered questionnaire	Maternal age	Age gender, region	Age and region of residence at diagnosis, gender,	Infectious diseases in the first year of life, perinatal characteristics, including maternal age
Kamper-Jogensen (2008)	Matched 1:10 population controls retrieved from Scandinavian registries	Population	Cases: ~ 100 %, Controls: ~ 100 %	Yes	NR	Maternal, paternal age	Age at diagnosis, gender, birth cohort	None	Childcare attendance
Kaye (1991)	Matched 1:4 controls randomly selected from the computerized file of all live births in the State of Minnesota. Excluded: 12 controls weighing <1500 g at birth	Population	Cases: 100 %, Controls: 99 %	NR	Birth certificate and supplemental information form	Maternal, paternal age	Age	None	Multiple primary exposures including parental age
Knox (1983)	NR	Population	NR	NR	NR	Maternal age	1:1 on date of birth, gender, residence	None	Multiple primary exposures including maternal age
Kumar (2014)	Randomly selected	Population	NR	NR	Interview with mother	Maternal age	Individual 1:1 on age, sex, residence	None	History of fetal loss and radiography, pesticide exposure, drug intake, infections during pregnancy Exposure to pesticides during pregnancy
Larfors (2012)	Randomly selected population controls, born in the same calendar year as the case and resident in Sweden at the date of diagnosis	Population	Cases: 87 %, Controls: 91 %	No	Multi-Generation Register derived from Swedish population statistics	Maternal, paternal age	1:4 on year of birth, residence	Gender, Down's syndrome, other chromosomal aberrations, multiple birth, birth order, number of younger siblings, mutual adjustment for maternal/paternal age; also unadjusted odds ratios	Parental age

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
Laval (1988)	Non-leukemic children admitted on the same date and hospital as cases for a diagnosis of a non-tumor serious illness	Hospital	NR	No	Questionnaire-based in-person or telephone interview with families by the same interviewer for each case–control pair; analysis of hospital records	Maternal, paternal age	Age, gender, nationality (except N. African)	None	Environmental factors
MacArthur (2008)	Randomly selected from the provincial government health insurance rolls	Population	Cases: 90 %, Controls: 76 %	Yes	Standardized questionnaire-based in person interview with both parents by trained interviewers; interviewers blinded to case–control status	Maternal, paternal age	1:1 on age, gender, residence	None	Parental smoking and alcohol consumption prior to conception and during pregnancy
Manning (1957)	Randomly selected from the orthopedic clinic of the Children's Medical Center in Boston; poliomyelitis excluded	Hospital	NR	NR	Question sheet-based interview of mother by the same interviewer	Maternal age	None	None	Multiple primary exposures including maternal age
McLaughlin (1993)	Identified from birth certificates; excluded: children who died before the date of their associated case's diagnosis	Population	Cases: ~ 98 %, Controls: 99 %	NR	Birth certificates	Maternal age	1:8 on date of birth, residence at birth	None	Paternal radiation exposure
Mertens (1998)	Population subjects selected by modified random digit dialing method	Population (Regional)	Cases: 89 %, Controls: 77 %	No	Telephone interview with mother by trained interviewers	Maternal, paternal age	Individual 1:1 matching on telephone exchange, age in all, and race in 2/3 of study arms	None	Congenital abnormalities
Milne (2010)	Recruited by national random digit dialing	Population	Cases: 75 %, Controls: 64 %	No	Mailed, self- administered questionnaires	Maternal age	Approximately 1:3 matching on age, gender, residence	None	Maternal folate and other vitamin supplementation during pregnancy
Milne (2012)	Recruited by national random digit dialing	Population	Cases: 75 %, Controls: 64 %	No	Self-administered questionnaires completed by both parents; brief telephone interview of mothers who did not complete the questionnaire	Paternal age	Approximately 1:2 matching on age, gender, residence	None	Parental prenatal smoking
Monge (2007)	Population controls, drawn from the National Birth Registry, with the use of computerized random selection	Neighborhood	Cases: 90 %, Controls: 91 %	NR	In-person interview with the parents, using an interview or icon-calendar form	Maternal age	Frequency matching on birth year	None	Pesticides exposure

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
NARECHEM (1996–2013)	Children hospitalized in the same hospitals for minor ailments at approximately the same time of leukemia or lymphoma diagnosis	Hospital	Cases: 97 %, Controls: 96 %	Yes	Structured questionnaire-based interviews with parents/guardians by trained interviewers	Maternal, paternal age	1:1 on age, gender	Parental socioprofessional status, birth weight, maternal smoking during pregnancy, mutual (and unmutual) adjustment for maternal and paternal age	Parental age
Oksuzyan (2012)	Children without history of cancer, randomly selected from the California Birth Registry	Population (birth registry)	Cases: 87 %, Controls: NR	No	Extracted from California birth records	Maternal, paternal age	Date of birth, gender	Maternal and paternal age <25 years and Incremental: birth order, father's education, child's race, and payment source for delivery, terminations after 20 weeks of gestation (maternal only); Other: none	Birth weight and other perinatal characteristics, including parental age
Pedersen (2014)	Incidence density sampling from the population-based Danish Civil Registration System; born alive in Denmark, cancer-free, living in Denmark at the time of diagnosis	Population	Cases: 86 %, Controls: 88 %	NR	Linkage with the Danish Civil Registration System, using the personal identification number	Maternal age	Individual 1:2 matching on year of birth, gender	None	Distance to High-Voltage Power Lines
Perez-Salvidar (2008)	Short-stay surgical patients at secondary-care hospitals that had referred children with LEUK to tertiary-care hospitals; live with both biological parents	Hospital	Cases: 88 %, Controls: 83 %	NR	Questionnaire-based in-person interview with both parents by trained personnel blinded as to study hypothesis	Maternal, paternal age	1:1 age, gender, institution of origin	None	Paternal occupational exposure to carcinogens
Perillat (2001)	Children hospitalized in the same hospital (mainly in orthopedic departments), residing in the same area as the cases; excluded: cancer, birth defect; adopted, incomplete questionnaire	Hospital	Cases: 99 %, Controls: NR	No	Standard questionnaire-based in-person interview with mother by trained medical interviewers	Maternal, paternal age	None	Maternal and paternal age <25: age, gender, hospital, and ethnic origin; Other: none	Family cancer history

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
Petridou (1997a)	Hospitalized for acute conditions at the same time as the corresponding cases	Hospital	Cases: 100 %, Controls 96 %	Yes	Interviewer-administered questionnaire responded by the guardians	Maternal age	Individual 1:2 matching on age, gender, residence	Maternal education, sibship size and birth order, ever-attendance of day care, maternal smoking and alcohol consumption during the index pregnancy, pet ownership at any time before diagnosis, anemia during pregnancy, neonatal jaundice, birth weight, hospitalization for any allergic disease, BCG vaccination, total DTP shots, total viral vaccination shots	Electrical power lines
Petridou (1997b)	Hospitalized for acute conditions at the same time as the corresponding cases	Hospital	Cases: 94 %, Controls: 92 %	Yes	Interviewer-administered questionnaire responded by the guardians	Maternal age	Individual 1:2 matching on age, gender, residence	None	Multiple primary exposures including maternal age
Petridou, Swedish arm (2012)	Randomly selected from Swedish Birth Registry, alive at the date of diagnosis of the respective case. Information from Death Register allowed censoring at death and thereby precise incidence density sampling of controls	Population (Birth registry)	Cases: ~100 %, Controls: 98 %	NR	Swedish Birth Registry	Maternal age	1:10 on age, gender	None	In-vitro fertilization
Podvin (2006)	Randomly selected from birth certificate records of children without LEUK	Population	NR	No	Birth certificates	Maternal age	Frequency matching on birth year	None	Maternal and birth characteristics, including maternal age
Puumala (2010)	Phase I: selected though random digit dialing; phase II: state birth registries; biological mother spoke English or Spanish (phase II), and was available by telephone	Population (regional)	Cases: 64 %, Controls: 46 %	Yes	Maternal telephone interview	Maternal age	Frequency matching on year of birth, residence	Year of birth, maternal education, race, smoking during pregnancy, household income, gestational age and birth weight	Parental infertility or its treatment

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
Roman (2005)	Randomly recruited from primary care population centers	Population	Cases: ~86 %, Controls: 78 %	No	Structured questionnaire-based in-person (alternatively telephone) interview with the parents; access of medical records	Maternal age	1:2 month/year of birth, gender, residence	Age, gender, study region	Multiple primary exposures including maternal age
Roman UK arm (2013)	Randomly selected from population registers	Population	Cases: 87 %, Controls 64 %	Yes	Interview with mother	Maternal age	1:2 on age, gender, residence	None	Birth weight
Roman German arm (2013)	Randomly selected from population registers	Population	Cases 82 %, Controls 69 %	Yes	Interview with mother	Maternal age	1:1 on age, gender, residence	None	Birth weight
Rubin (2007)	Identified through random-digit dialing; cancer-free at the date of the case child's diagnosis; parents/guardians/other care-taking adults living full time in the comparison child's home	Population	Cases: 93 %, Controls: 44 %	NR	Mailed questionnaires; in-person interview with parents	Paternal age	1:4 on birth year, gender	None	Chemical exposures
Rudant (2012)	Population-based, randomly selected by quota sampling method, cancer-free; excluded: adopted, biological mother had died, non-French-speaking, had a serious psychiatric disorder	Population	Cases: 91 %, Controls: 71 %	No	Structured questionnaire-based telephone interview with the mother, by the same trained interviewers as cases	Maternal age	Frequency matching on age, gender	Stratification variable age × gender	Fertility treatments, congenital malformations, fetal loss
Rudant (2010)	Population-based, randomly selected by quota sampling method, cancer-free; excluded: chromosomal abnormalities, adopted, biological mother had died, non-French-speaking, had a serious psychiatric disorder	Population	Cases: 91 %, Controls: 71 %	Yes	Structured questionnaire-based telephone interviews with the mother, by the same trained interviewers as cases	Maternal age	Frequency matching on age, gender	Stratification variable age × gender	Early infections and allergy
Salonen (1975)	Children born immediately before the study cases in the same Maternity Welfare District; information collected in the same way as cases	Population (maternity welfare organisation)	Cases: ~99 %, Controls: ~96 %	NR	Records of Maternity Welfare Centers and questionnaire sent to the maternity hospitals	Maternal age	1:1 on age, season of birth, residence	None	Multiple primary exposures including maternal age

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
Schlehofer (1996)	Treated in the participating hospitals for other reasons; inclusion criteria same as cases; excluded: tumors, B-19 infection	Hospital	Cases: 52 %, Controls: 92 %	No	Self-administered questionnaire	Paternal age	Frequency matching on age, gender	Number of children, housing, place of residence, person who answered the questionnaire, parental educational level, mutual (and unmutual) adjustment between maternal and paternal age	Virus infections
Schuz (1999)	NW: Randomly selected from complete files of local offices for registration of residents NI: living in a matched control region	Population (regional)	Cases: 81 %, Controls: 65 %	No	Mailed structured questionnaire validated by telephone interview with both parents, where possible, by trained interviewers	Maternal age	1:1 on: NW: date of birth, gender, district where the case lived at the date of diagnosis NI: control region	None	Multiple primary exposures including maternal age
Shu (1988)	Randomly selected from the Shanghai general population; adopted substituted	Neighborhood	Cases: 93 %, Controls: ~100 %	No	In-person interview with parents or other relatives	Maternal, paternal age	1:2 on birth year, gender	Maternal age $\leq$ 25 and paternal age $\leq$ 27: age, gender, birth weight, birth order, born in rural area, prenatal and paternal preconception x-ray exposure, chloramphenicol and syntomycin usage, mother's age at menarche, and maternal occupational exposure during pregnancy; Other: none	Multiple primary exposures including parental age
Shu (1994)	Randomly selected from the general population of urban Shanghai; excluded: cancer, adopted, living with guardians other than the natural parents	Population	Cases: 78 %, Controls: 94 %	NR	Structured questionnaire-based interview with both parents by trained retired nurses	Maternal age	1:1 on year of birth, gender	None	Diagnostic X-ray and ultrasound
Sprehe (2010)	Subjects drawn from the residual (non-matched) Texas birth files; no known cancer cases were selected as controls, although there is the possibility that an unmatched case was selected; excluded: birth weight missing or <500 grams, congenital conditions likely to cause death during infancy	Population	Cases: ~74 %, Controls: ~100 %	Maternal age $\geq$ 35 AML and paternal age $\geq$ 35: Yes; Other: No	Birth certificates	Maternal age paternal age	Frequency 5:1 matching on birth year	Maternal age $\geq$ 35 for ALL and LEUK: Birth weight, gender, ethnicity, birth year, gestational age; Other: none	Birth Weight

Table 1 continued

Author (year)	Definition/features of controls–exclusion criteria	Source of control selection	Participation rate	Down's syndrome excluded	Ascertainment source of information on parental age	Age indices synthesized	Matching ratio/variables	Adjusting variables	Primary exposure of interest in study
Thompson (2001)	Randomly selected from the state electoral roll	Population	Cases:82 %, Controls: 74 %	NR	Interview with mother consisted of about 180 questions, conducted by a nurse	Maternal age	1:2 on date of birth, gender, residence	None	Multiple primary exposures including maternal age
Untario (1972)	Retrieved from data of "healthy" mothers and babies born at the same hospital as cases	Population (Obstetric Department)	Cases: 91 %, Controls: NR	No	Retrieved from available case histories, self-reported, or judged by the doctors or the nurses	Maternal age	None	None	Maternal age
van Duijn, ANLL arm (1994)	Randomly selected from the municipal registration of the matched case	Population	Cases: 86 %, Controls: 66 %	NR	Three standard questionnaires mailed to the parents	Maternal age	1:3 on age, gender	Year of birth, gender, social class, alcohol, smoking, occupational exposure to hydrocarbons, drugs, ultrasound, radiation, viral infections	Maternal alcohol consumption
van Steensel-Moll (1985)	Randomly selected from the municipal registration of the matched case	Population	Cases: 83 %, Controls: 70 %	NR	Self-administrated questionnaires mailed to the parents	Maternal age	1:2 on year of birth, gender, residence	Age, gender	Maternal fertility problems
Wen (1998)	Randomly selected using random-digit-dialing method; existence of a telephone in the control's residence; biological mother available for interview, English-speaking	Population	Cases 79 %, Controls 75 %	NR	Structured questionnaire-based telephone interview with mother (and fathers whenever available)	Maternal, paternal age	Individual 1:2 matching on year of birth, telephone area code and exchange	Maternal and paternal age <25: parental education of the parents, family income gender of the index child, mutual adjustment for parental age; Other: none	Family history of cancer and autoimmune disease
Wong (2006)	Randomly selected from nationwide birth registry	Population (Birth registry)	Cases: 78 %, Controls: NR	NR	Birth records	Maternal, paternal age	1:1 on quarter and year of birth, gender	Social class	Birth characteristics, including maternal age

ALL Acute lymphoblastic leukemia, *AML* Acute myeloid leukemia, *APL* acute promyelocytic leukemia, *FHSA* family health services authority, *LEUK* leukemia, *NR* not reported, *NRCT* national registry of childhood tumors, *NI* nuclear installations part of the study, *NW* nationwide part of the study, *UKCCSG* united kingdom childhood cancer study group

[a] Corresponds to the total sample size, as it was not provided for the sample(s) retained for this meta-analysis

Table 2 Characteristics of the eight eligible cohort studies

Author (year)	Cohort size	Incident cases	Follow-up (years, median/mean)	Study period	Region	Males (%)	Mean age (years)	Age range (years)	Cohort Characteristics-exclusion criteria
Hemminki (1999)	~6 million	1427 LEUK	NR	1940–1994	Sweden	NR	NR	<15	The Second Generation Register includes children born in Sweden in 1940 and later, and their biological parents
MacMahon (1962)	734,243	304 LEUK	NR	1947–1960	Northeast Region, USA	NR	NR	0–13	Children born in and discharged alive from 37 large maternity hospitals in the years 1947–54
Maule (2007a)	>500,000	252 ALL	NR	1980–1997	Piedmont, Italy	NR	NR	1–5	Piedmont childhood population
Maule (2007b)	633,155	229 ALL	NR	1980–2002	Piedmont, Italy	NR	NR	0–5	Piedmont childhood population
Murray (2002)	434,933	188 ALL	NR	1971–1997	Northern Ireland	51.51	5.26	<16	All births to mothers normally resident in Northern Ireland during 1971–1986 obtained from Northern Ireland Child Health System birth records; multiple births excluded
Stark (1966)	2,837,093	706 LEUK	NR	1950–1964	Michigan, USA	NR	NR	0–15	All Michigan live births during 1950–64 obtained from National Office of Vital Statistics, the National Center for Health Statistics, and the Michigan State Department of Health
Sung (2008)	40,647	15 LEUK	15.72	1978–2001	Taiwan	51.87	NR	NR	All live born children of female electronic factory workers and their birth related data identified from linkage of female workers' identification numbers with the Taiwan Birth Registration database during 1978–2001; first singletons
Westergaard (1997)	1,975,584	704 ALL; 114 AML	10.58	1968–1992	Denmark	NR	NR	0–14	All Denmark live births during 1968–1992 retrieved from Danish Civil Registration System; Down's syndrome excluded

Table 2 continued

Author (year)	Definition/features of leukemia	Type of cases	Case ascertainment	Participation rate	Down's syndrome excluded	AscertainmentSource of information on parental age	Age indices synthesized	Adjusting factors	Primary exposure of interest in study
Hemminki (1999)	First primary LEUK cases retrieved through linkage of Second Generation Register to the nationwide Swedish Cancer Registry; linked records checked for identification and reasonable age at child birth; age data available for both parents	Incident	Registry-based	~100 %	NR	Retrieved from linked records	Maternal, paternal age	Period of birth, birth order, mutual (and unmutual) adjustment for maternal/paternal age	Parental age
MacMahon (1962)	LEUK deaths identified by review of death and birth certificates in the Northeast Region	Mortality	Death and birth certificates	~100 %	NR	NR	Maternal age	None	Prenatal X-Ray Exposure
Maule (2007a)	ALL cases identified from population-based Childhood Cancer Registry	Incident	Registry-based	~100 %	NR	Retrieved from Childhood Cancer Registry	Maternal age	None	Maternal age
Maule (2007b)	ALL cases identified from population-based Childhood Cancer Registry	Incident	Registry-based	~100 %	NR	Retrieved from Cancer Registry of Piedmont and National Institute of Statistics	Maternal, paternal age	Gender, year of birth, mutual (and unmutual) adjustment for paternal/maternal age	Parental age
Murray (2002)	ALL cases identified from Northern Ireland Cancer Registry; additional data obtained from the Oxford Childhood Cancer Register; clinicians' records and; databases of specific research projects into childhood cancer.	Incident	Registry-based	98 %	No	Retrieved from Department of Health, Social Services and Public Safety birth records	Maternal, paternal age	Maternal age $\geq$ 35: gender, Down's syndrome, history of miscarriage, gestational age, birth weight, social class, three or more adults in the household, household density, mutual adjustment for maternal/paternal age; Other: none	Multiple primary exposures including parental age
Stark (1966)	Leukemia deaths ascertained from state-wide death records	Mortality	Death certificates	NR	No	Retrieved from birth certificates	Maternal age	None	Maternal age

Table 2 continued

Author (year)	Definition/features of leukemia	Type of cases	Case ascertainment	Participation rate	Down's syndrome excluded	AscertainmentSource of information on parental age	Age indices synthesized	Adjusting factors	Primary exposure of interest in study
Sung (2008)	ALL cases retrieved by linkage of Taiwan Birth Registry to National Cancer Registry	Incident	Registry-based	~86 %	NR	Retrieved from linkage of female workers' identification numbers with the Taiwan Birth Registry	Maternal age	Gender, year of birth, educational level, periconceptual exposure to potential organic solvents	Maternal periconceptional occupational exposure
Westergaard (1997)	ALL, AML cases identified by linkage of Danish Civil Registration System to Danish Cancer Registry	Incident	Registry-based	~100 %	Yes	Retrieved from the Civil Registration System	Maternal, paternal age	Age, gender, calendar period, birth order	

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *LEUK* leukemia, *NR* not reported

was reproducible among the subset of case–control studies, as well studies published in the Americas. The paucity of effect estimates with mutual adjustment between maternal and paternal age became evident, as only three studies adopted such a design (Supplemental Figure 5). Sensitivity analyses according to the cut-off adopted (Supplemental Figure 6) indicated persistence of the positive association among studies setting the cut-off at 35 years (pooled RR = 1.14, 95 % CI 1.02–1.27); however, only five studies adopted a cut-off point at 40 years and their pooling yielded a sizable but non-significant effect estimate (pooled RR = 1.27, 95 % CI 0.89–1.81).

The "youngest versus middle" comparison did not point to nominally significantly increased risk for ALL among youngest mothers (pooled RR = 1.09, 95 % CI 0.99–1.19, p = 0.077). No consistently significant associations arose in subgroup analyses, including the sensitivity analysis examining the extreme age category of women giving birth prior to 20 years of age (Supplemental Figures 7–10).

Maternal age and risk for AML

The lower parts of Table 3 present the results of meta-analyses on the association of maternal age and risk of AML. The overall pattern showed a U-shaped association, as both oldest (pooled RR = 1.23, 95 % CI 1.06–1.43, Fig. 2a) and youngest extremes (pooled RR = 1.23, 95 % CI 1.07–1.40, Fig. 2b) were symmetrically associated with increased risk for AML; consequently, the incremental analysis was close to the null value of one (pooled RR = 1.02, 95 % CI 0.95–1.10).

Subgroup and sensitivity analyses were rather hampered by the small number of study arms; it seems however worth noting that regarding oldest age (Supplemental Figures 11–13), the association was reproducible among high-quality studies. Moreover, only three studies examined age categories older than 40 years and yielded a sizable but non-significant effect estimate (pooled RR = 1.99, 95 % CI 0.45–8.89). Concerning youngest age (Supplemental Figures 14–15), the sizable association with AML risk persisted among studies with adjusted effect estimates, including those with mutual adjustment between maternal and paternal age. Regarding incremental analyses, the null association persisted except for an association in non-adjusted studies (Supplemental Figure 16).

Paternal age and risk for ALL

The upper parts of Table 4 present the results pertaining to the association between paternal age and risk of ALL. The incremental analysis suggested a positive association between older paternal age and increased risk for childhood ALL (pooled RR = 1.04, 95 % CI 1.00–1.08, per 5 years,

Table 3 Results of the meta-analyses examining the association between maternal age and risk of childhood leukemia

	"Oldest versus middle" comparison			"Youngest versus middle" comparison			Maternal age in increments		
	n[a]	RR (95 % CI)	Heterogeneity I^2, p	n[a]	RR (95 % CI)	Heterogeneity I^2, p	n[a]	RR (95 % CI)	Heterogeneity I^2, p
Analysis on ALL									
Overall analysis	36	**1.10 (1.00–1.21)**	45.7 %, 0.002	31	1.09 (0.99–1.19)	55.8 %, <0.001	12	**1.05 (1.01–1.10)**	72.0 %, <0.001
Subgroups by study design									
Case–control studies	29	**1.11 (1.00–1.23)**	54.2 %, <0.001	24	1.11 (1.00–1.23)	62.5 %, <0.001	10	1.04 (0.99–1.08)	69.2 %, 0.001
Cohort studies	7	1.15 (0.84–1.57)	0.0 %, 0.802	7	0.96 (0.79–1.17)	0.0 %, 0.646	2	**1.18 (1.01–1.38)**	64.1 %, 0.095
Subgroups by geographic region									
Europe	22	1.02 (0.93–1.12)	23.5 %, 0.157	21	1.10 (0.97–1.24)	63.7 %, <0.001	6	**1.09 (1.03–1.14)**	52.4 %, 0.062
USA/Canada	5	**1.43 (1.19–1.73)**	10.6 %, 0.346	3	0.96 (0.82–1.11)	0.0 %, 0.580	4	1.02 (0.95–1.09)	80.2 %, 0.002
Asia	3	0.92 (0.63–1.35)	0.0 %, 0.909	3	0.91 (0.56–1.48)	47.4 %, 0.149	0	No studies	
Australia–NZ	5	1.10 (0.74–1.64)	71.2 %, 0.008	4	**1.19 (1.05–1.34)**	0.0 %, 0.882	2	0.95 (0.82–1.10)	0.0 %, >0.999
Latin America	1	**3.72 (1.13–12.27)**	NC	0	No studies		0	No studies	
Subgroups by degree of adjustment									
No adjustment	23	1.12 (0.99–1.27)	41.3 %, 0.021	21	1.07 (0.98–1.18)	37.2 %, 0.045	3	**1.09 (1.05–1.14)**	0.0 %, 0.547
Adjustment—no mutual adjustment for maternal and paternal age	10	1.16 (0.92–1.47)	64.4 %, 0.003	8	1.19 (0.94–1.49)	75.2 %, <0.001	6	1.03 (0.97–1.09)	73.1 %, 0.002
Mutual adjustment for maternal and paternal age	3	0.97 (0.84–1.12)	0.0 %, 0.894	2	0.81 (0.36–1.81)	84.2 %, 0.012	3	1.09 (0.96–1.24)	76.1 %, 0.015
Subgroups by overall study quality									
Low (NOS 1–3)	0	No studies		0	No studies		0	No studies	
Intermediate (NOS 4–6)	12	1.17 (0.95–1.43)	65.5 %, 0.001	9	**1.20 (1.10–1.30)**	0.0 %, 0.855	1	0.90 (0.74–1.11)	NC
High (NOS 7–9)	24	1.08 (0.97–1.20)	29.4 %, 0.088	22	1.01 (0.88–1.16)	64.0 %, <0.001	11	**1.06 (1.01–1.10)**	73.6 %, <0.001
Sensitivity analyses about older age									
Sensitivity analysis, with cut-off set at 35 years	33	**1.14 (1.02–1.27)**	45.6 %, 0.003		Not applicable			Not applicable	
Sensitivity analysis, with cut-off set at 40 years	5	1.27 (0.89–1.81)	15.3 %, 0.317		Not applicable			Not applicable	
Sensitivity analysis about younger age									
Sensitivity analysis, with cut-off set at 20 years		Not applicable		9	1.09 (0.94–1.27)	36.2 %, 0.129		Not applicable	
Analysis on AML									
Overall analysis	20	**1.23 (1.06–1.43)**	0.0 %, 0.553	18	**1.23 (1.07–1.40)**	0.0 %, 0.767	9	1.02 (0.95–1.10)	45.9 %, 0.064
Subgroups by study design									
Case–control studies	19	**1.24 (1.06–1.44)**	0.0 %, 0.516	17	**1.23 (1.07–1.41)**	0.0 %, 0.707	8	1.03 (0.96–1.11)	49.6 %, 0.053
Cohort studies	1	0.85 (0.28–2.57)	NC	1	1.26 (0.62–2.57)	NC	1	0.90 (0.70–1.17)	NC

Table 3 continued

	"Oldest versus middle" comparison			"Youngest versus middle" comparison			Maternal age in increments		
	n[a]	RR (95 % CI)	Heterogeneity I^2, p	n[a]	RR (95 % CI)	Heterogeneity I^2, p	n[a]	RR (95 % CI)	Heterogeneity I^2, p
Subgroups by geographic region									
Europe	12	1.10 (0.91–1.34)	0.0 %, 0.956	11	**1.26 (1.06–1.51)**	0.0 %, 0.576	4	0.92 (0.84–1.01)	0.0 %, 0.887
USA/Canada	3	1.93 (0.92–4.03)	46.2 %, 0.156	2	1.03 (0.64–1.67)	0.0 %, 0.336	4	1.10 (0.99–1.23)	62.0 %, 0.048
Asia	2	1.37 (0.82–2.30)	0.0 %, 0.323	2	1.38 (0.81–2.34)	0.0 %, 0.563	0	No studies	
Australia–NZ	3	1.14 (0.78–1.68)	0.0 %, 0.545	3	1.19 (0.93–1.51)	0.0 %, 0.394	1	1.05 (0.76–1.45)	NC
Latin America	0	No studies		0	No studies		0	No studies	
Subgroups by degree of adjustment									
No adjustment	10	1.31 (0.98–1.76)	23.7 %, 0.225	7	1.16 (0.95–1.41)	0.0 %, 0.653	2	**1.21 (1.08–1.36)**	0.0 %, 0.963
Adjustment—no mutual adjustment for maternal and paternal age	8	1.24 (0.95–1.62)	0.0 %, 0.859	9	**1.22 (1.00–1.49)**	0.0 %, 0.725	5	1.01 (0.98–1.05)	0.0 %, 0.728
Mutual adjustment for maternal and paternal age	2	1.00 (0.72–1.39)	0.0 %, 0.568	2	**1.81 (1.11–2.93)**	0.0 %, 0.600	2	0.89 (0.77–1.02)	0.0 %, 0.735
Subgroups by overall study quality									
Low (NOS 1–3)	0	No studies		0	No studies		0	No studies	
Intermediate (NOS 4–6)	8	1.05 (0.82–1.35)	0.0 %, 0.980	7	**1.19 (1.00–1.41)**	0.0 %, 0.779	1	1.05 (0.86–1.28)	NC
High (NOS 7–9)	12	**1.37 (1.09–1.72)**	18.9 %, 0.258	11	**1.29 (1.04–1.60)**	0.0 %, 0.538	8	1.02 (0.94–1.10)	52.4 %, 0.040
Sensitivity analyses about older age									
Sensitivity analysis, with cut-off set at 35 years	18	**1.21 (1.03–1.43)**	0.9 %, 0.444		Not applicable			Not applicable	
Sensitivity analysis, with cut-off set at 40 years	3	1.99 (0.45–8.89)	31.5 %, 0.232		Not applicable			Not applicable	
Sensitivity analysis about younger age									
Sensitivity analysis, with cut-off set at 20 years		Not applicable		6	1.16 (0.85–1.59)	0.0 %, 0.468		Not applicable	

Bold cells denote statistically significant associations

[a] Number of study arms, *NC* not calculable, *NOS* Newcastle–Ottawa score

Fig. 3), which was particularly evident among high-quality, case–control and European studies, which at any case represented the majority of eligible study arms. Similarly to maternal age, this association was significant among unadjusted studies (pooled RR = 1.09, 95 % CI 1.00–1.19, Supplemental Figure 17).

The "oldest versus middle" comparison pointed to increased risk for childhood ALL among offspring from oldest fathers (pooled RR = 1.10, 95 % CI 1.02–1.19, Supplemental Figures 18–20); this was reproducible in high-quality, case–control, European and unadjusted studies, which represented the majority of synthesized data. Sensitivity analyses on the adopted cut-off (Supplemental Figure 20) indicated persistence of the positive association among studies setting the cut-off at 35 years (pooled RR = 1.12, 95 % CI 1.03–1.21), whereas only five studies set a cut-off value at 40 years or older and did not point to a sizable association.

The "youngest versus middle" comparison suggested a marginally elevated risk for ALL among youngest fathers (pooled RR = 1.09, 95 % CI 1.00–1.20), which was mainly due to case–control, intermediate-quality and unadjusted studies (Supplemental Figures 21–23).

Paternal age and risk for AML

The results of meta-analyses on the association between paternal age and risk of AML are presented in the lower parts of Table 4. No significant association was documented either at the incremental analysis (pooled RR = 1.04, 95 % CI 0.98–1.09, Supplemental Figures 24–25) or at the "oldest versus middle" comparison (pooled RR = 1.05, 95 % CI 0.87–1.26, Supplemental Figures 26–28). On the other hand, increased risk for AML was noted in offspring from younger fathers (pooled RR = 1.28, 95 % CI 1.04–1.59, Supplemental Figures 29–31); this association was evident in case–control, intermediate-quality and unadjusted studies.

Risk for leukemia in studies with mixed reporting

Supplemental Table 1 (Supplemental Figures 32–34) presents the results of meta-analyses examining the association between maternal/paternal age and risk of leukemia in studies with mixed reporting of subtypes. Given the admixture of subtypes and superimposition of patterns, no consistent associations were observed, except for a positive association between maternal age and risk of leukemia in the incremental analysis.

Fig. 2 Forest plot describing the association between risk for childhood AML and maternal age **a** oldest versus middle; **b** youngest versus middle analysis. Apart from the overall analysis, the sub-analyses on case–control (*upper panels*) and cohort (*lower panels*) studies are presented

Additional sensitivity analysis removing studies with partial overlap

The results of the additional sensitivity analysis removing studies with partial overlap are depicted in Supplemental Figures 35–38. The documented associations persisted during this approach, as a rule.

Evaluation of quality of studies, meta-regression analysis and risk of bias

The evaluation of quality of studies is presented in Supplemental Table 2. Notions that led to decreased quality of

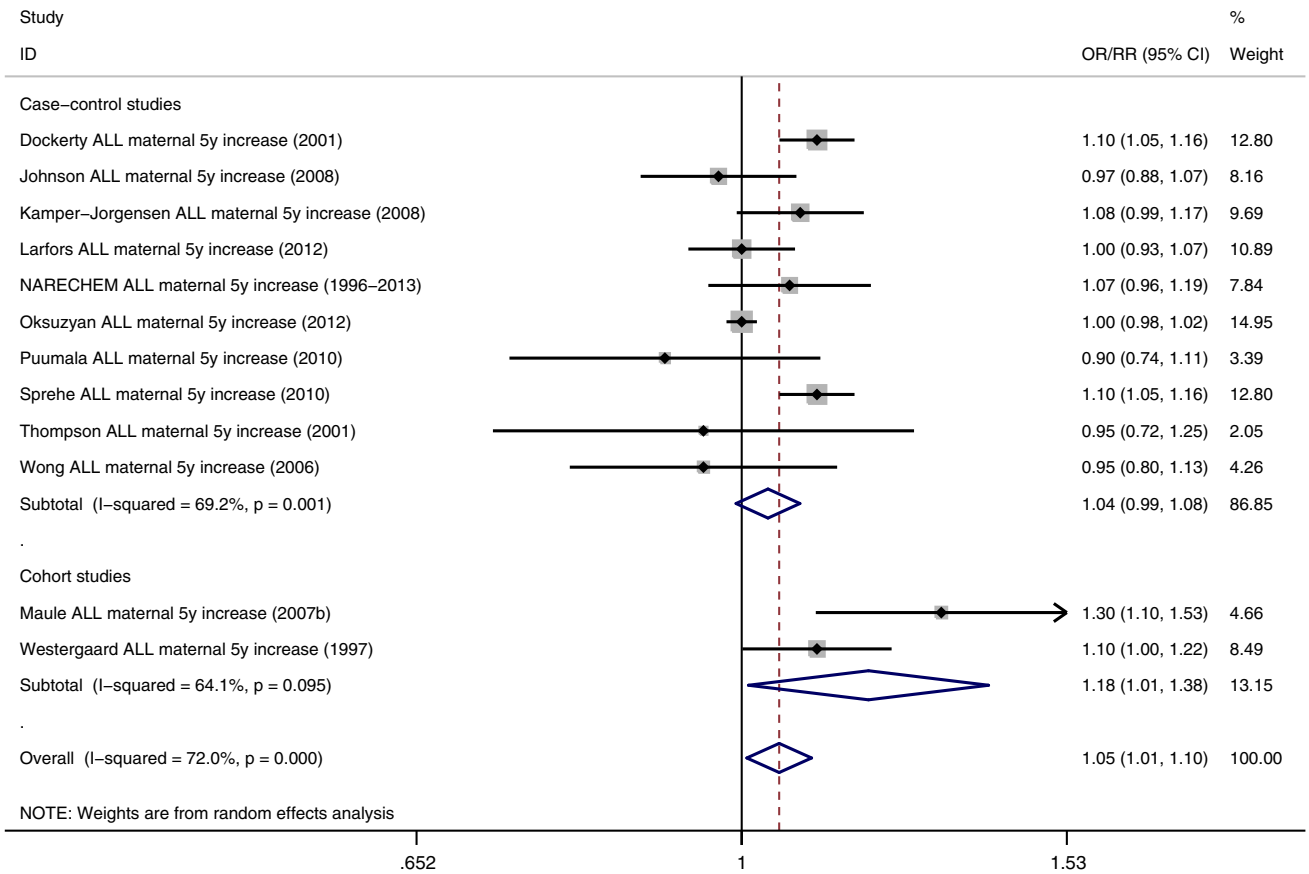

Fig. 1 Forest plot describing the association between risk for childhood ALL and maternal age (incremental analysis). Apart from the overall analysis, the sub-analyses on case–control (*upper panels*) and cohort (*lower panels)* studies are presented

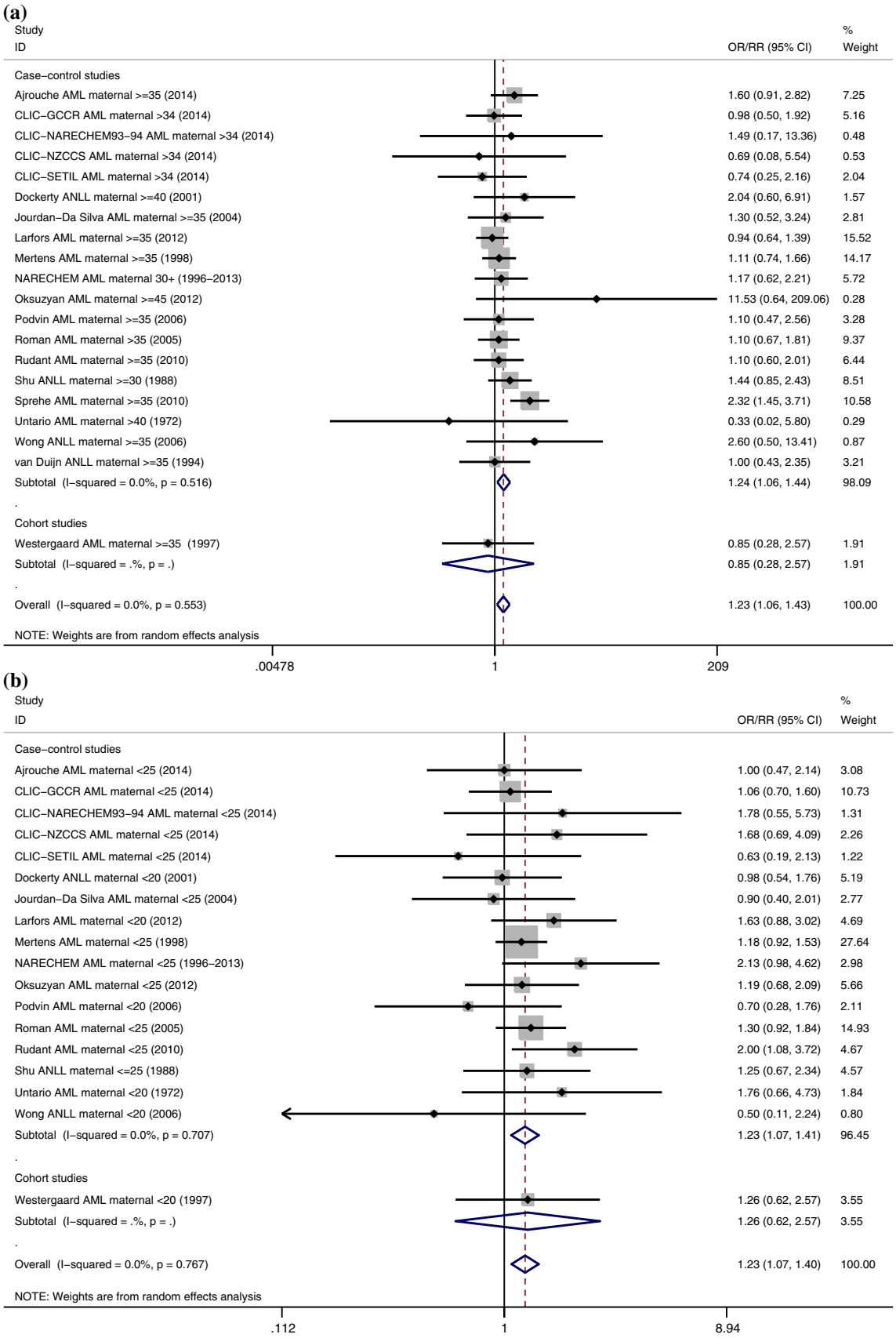
(a)
Study ID
OR/RR (95% CI)
% Weight
Case–control studies
Ajrouche AML maternal >=35 (2014) 1.60 (0.91, 2.82) 7.25
CLIC–GCCR AML maternal >34 (2014) 0.98 (0.50, 1.92) 5.16
CLIC–NARECHEM93–94 AML maternal >34 (2014) 1.49 (0.17, 13.36) 0.48
CLIC–NZCCS AML maternal >34 (2014) 0.69 (0.08, 5.54) 0.53
CLIC–SETIL AML maternal >34 (2014) 0.74 (0.25, 2.16) 2.04
Dockerty ANLL maternal >=40 (2001) 2.04 (0.60, 6.91) 1.57
Jourdan–Da Silva AML maternal >=35 (2004) 1.30 (0.52, 3.24) 2.81
Larfors AML maternal >=35 (2012) 0.94 (0.64, 1.39) 15.52
Mertens AML maternal >=35 (1998) 1.11 (0.74, 1.66) 14.17
NARECHEM AML maternal 30+ (1996–2013) 1.17 (0.62, 2.21) 5.72
Oksuzyan AML maternal >=45 (2012) 11.53 (0.64, 209.06) 0.28
Podvin AML maternal >=35 (2006) 1.10 (0.47, 2.56) 3.28
Roman AML maternal >35 (2005) 1.10 (0.67, 1.81) 9.37
Rudant AML maternal >=35 (2010) 1.10 (0.60, 2.01) 6.44
Shu ANLL maternal >=30 (1988) 1.44 (0.85, 2.43) 8.51
Sprehe AML maternal >=35 (2010) 2.32 (1.45, 3.71) 10.58
Untario AML maternal >40 (1972) 0.33 (0.02, 5.80) 0.29
Wong ANLL maternal >=35 (2006) 2.60 (0.50, 13.41) 0.87
van Duijn ANLL maternal >=35 (1994) 1.00 (0.43, 2.35) 3.21
Subtotal (I–squared = 0.0%, p = 0.516) 1.24 (1.06, 1.44) 98.09
Cohort studies
Westergaard AML maternal >=35 (1997) 0.85 (0.28, 2.57) 1.91
Subtotal (I–squared = .%, p = .) 0.85 (0.28, 2.57) 1.91
Overall (I–squared = 0.0%, p = 0.553) 1.23 (1.06, 1.43) 100.00
NOTE: Weights are from random effects analysis
.00478
1
209
(b)
Study ID
OR/RR (95% CI)
% Weight
Case–control studies
Ajrouche AML maternal <25 (2014) 1.00 (0.47, 2.14) 3.08
CLIC–GCCR AML maternal <25 (2014) 1.06 (0.70, 1.60) 10.73
CLIC–NARECHEM93–94 AML maternal <25 (2014) 1.78 (0.55, 5.73) 1.31
CLIC–NZCCS AML maternal <25 (2014) 1.68 (0.69, 4.09) 2.26
CLIC–SETIL AML maternal <25 (2014) 0.63 (0.19, 2.13) 1.22
Dockerty ANLL maternal <20 (2001) 0.98 (0.54, 1.76) 5.19
Jourdan–Da Silva AML maternal <25 (2004) 0.90 (0.40, 2.01) 2.77
Larfors AML maternal <20 (2012) 1.63 (0.88, 3.02) 4.69
Mertens AML maternal <25 (1998) 1.18 (0.92, 1.53) 27.64
NARECHEM AML maternal <25 (1996–2013) 2.13 (0.98, 4.62) 2.98
Oksuzyan AML maternal <25 (2012) 1.19 (0.68, 2.09) 5.66
Podvin AML maternal <20 (2006) 0.70 (0.28, 1.76) 2.11
Roman AML maternal <25 (2005) 1.30 (0.92, 1.84) 14.93
Rudant AML maternal <25 (2010) 2.00 (1.08, 3.72) 4.67
Shu ANLL maternal <=25 (1988) 1.25 (0.67, 2.34) 4.57
Untario AML maternal <20 (1972) 1.76 (0.66, 4.73) 1.84
Wong ANLL maternal <20 (2006) 0.50 (0.11, 2.24) 0.80
Subtotal (I–squared = 0.0%, p = 0.707) 1.23 (1.07, 1.41) 96.45
Cohort studies
Westergaard AML maternal <20 (1997) 1.26 (0.62, 2.57) 3.55
Subtotal (I–squared = .%, p = .) 1.26 (0.62, 2.57) 3.55
Overall (I–squared = 0.0%, p = 0.767) 1.23 (1.07, 1.40) 100.00
NOTE: Weights are from random effects analysis
.112
1
8.94

Table 4 Results of the meta-analyses examining the association between paternal age and risk of childhood leukemia

	"Oldest versus middle" comparison			"Youngest versus middle" comparison			Paternal age in increments		
	n[a]	RR (95 % CI)	Heterogeneity I^2, p	n[a]	RR (95 % CI)	Heterogeneity I^2, p	n[a]	RR (95 % CI)	Heterogeneity I^2, p
Analysis on ALL									
Overall analysis	25	**1.10 (1.02–1.19)**	45.2 %, 0.008	22	**1.09 (1.00–1.20)**	25.6 %, 0.134	10	**1.04 (1.00–1.08)**	70.9 %, <0.001
Subgroups by study design									
Case–control studies	22	**1.09 (1.01–1.18)**	47.1 %, 0.008	19	**1.11 (1.01–1.22)**	33.0 %, 0.082	8	**1.04 (1.00–1.08)**	73.2 %, <0.001
Cohort studies	3	1.29 (0.99–1.70)	11.8 %, 0.322	3	0.94 (0.70–1.26)	0.0 %, 0.778	2	1.07 (0.98–1.17)	30.3 %, 0.231
Subgroups by geographic region									
Europe	14	**1.13 (1.05–1.23)**	26.2 %, 0.173	14	1.10 (0.97–1.24)	25.1 %, 0.184	6	**1.05 (1.02–1.08)**	0.0 %, 0.580
USA/Canada	4	1.19 (0.94–1.52)	72.1 %, 0.013	2	0.93 (0.82–1.06)	0.0 %, 0.911	3	1.07 (0.97–1.18)	88.0 %, <0.001
Asia	2	0.79 (0.57–1.09)	0.0 %, 0.425	2	1.17 (0.80–1.71)	15.3 %, 0.277	0	No studies	
Australia-NZ	4	0.96 (0.75–1.24)	47.9 %, 0.124	4	**1.24 (1.07–1.43)**	0.0 %, 0.863	1	0.86 (0.74–1.00)	NC
Latin America	1	0.93 (0.46–1.89)	NC	0	No studies		0	No studies	
Subgroups by degree of adjustment									
No adjustment	18	**1.09 (1.00–1.20)**	47.4 %, 0.014	14	**1.14 (1.00–1.29)**	41.8 %, 0.050	3	**1.09 (1.00–1.19)**	57.5 %, 0.095
Adjustment—no mutual adjustment for maternal and paternal age	3	1.21 (0.78–1.85)	60.6 %, 0.079	5	0.97 (0.86–1.09)	0.0 %, 0.834	4	1.03 (0.97–1.08)	75.0 %, 0.007
Mutual adjustment for maternal and paternal age	4	1.06 (0.90–1.25)	20.7 %, 0.286	3	1.10 (0.81–1.51)	0.0 %, 0.957	3	1.03 (0.98–1.08)	0.0 %, 0.520
Subgroups by overall study quality									
Low (NOS 1–3)	0	No studies		0	No studies		0	No studies	
Intermediate (NOS 4–6)	9	1.08 (0.98–1.20)	38.1 %, 0.114	8	**1.16 (1.01–1.35)**	44.3 %, 0.083	0	No studies	
High (NOS 7–9)	16	**1.12 (1.00–1.25)**	50.6 %, 0.011	14	1.00 (0.91–1.10)	0.0 %, 0.578	10	**1.04 (1.00–1.08)**	70.9 %, <0.001
Sensitivity analyses about older age									
Sensitivity analysis, with cut-off set at 35 years	23	**1.12 (1.03–1.21)**	47.7 %, 0.006		Not applicable			Not applicable	
Sensitivity analysis, with cut-off set at 40 years	5	0.97 (0.74–1.27)	55.9 %, 0.060		Not applicable			Not applicable	
Sensitivity analysis about younger age									
Sensitivity analysis, with cut-off set at 20 years		Not applicable		3	1.08 (0.81–1.44)	0.0 %, 0.934		Not applicable	
Analysis on AML									
Overall analysis	16	1.05 (0.87–1.26)	40.3 %, 0.048	15	**1.28 (1.04–1.59)**	34.5 %, 0.092	7	1.04 (0.98–1.09)	31.7 %, 0.186
Subgroups by study design									
Case–control studies	15	1.07 (0.88–1.29)	42.0 %, 0.044	14	**1.26 (1.01–1.56)**	35.0 %, 0.096	6	1.04 (0.98–1.11)	41.5 %, 0.128
Cohort studies	1	0.72 (0.33–1.58)	NC	1	2.38 (0.81–6.99)	NC	1	0.95 (0.76–1.19)	NC

Table 4 continued

	"Oldest versus middle" comparison			"Youngest versus middle" comparison			Paternal age in increments		
	n[a]	RR (95 % CI)	Heterogeneity I^2, p	n[a]	RR (95 % CI)	Heterogeneity I^2, p	n[a]	RR (95 % CI)	Heterogeneity I^2, p
Subgroups by geographic region									
Europe	10	0.96 (0.81–1.13)	0.1 %, 0.436	10	1.35 (0.96–1.91)	42.3 %, 0.076	4	1.02 (0.94–1.11)	0.0 %, 0.591
USA/Canada	2	1.70 (0.98–2.96)	58.9 %, 0.119	1	1.25 (0.89–1.75)	NC	2	1.06 (0.92–1.23)	82.0 %, 0.018
Asia	1	0.89 (0.54–1.45)	NC	1	0.83 (0.46–1.51)	NC	0	No studies	
Australia-NZ	3	1.21 (0.67–2.19)	27.2 %, 0.253	3	1.36 (0.82–2.26)	32.9 %, 0.225	1	1.16 (0.89–1.51)	NC
Latin America	0	No studies		0	No studies		0	No studies	
Subgroups by degree of adjustment									
No adjustment	11	1.10 (0.89–1.36)	42.1 %, 0.068	8	**1.51 (1.13–2.02)**	39.2 %, 0.118	1	**1.16 (1.03–1.31)**	NC
Adjustment—no mutual adjustment for maternal and paternal age	3	1.37 (0.54–3.45)	51.5 %, 0.127	5	1.17 (0.90–1.52)	0.0 %, 0.443	4	1.00 (0.98–1.02)	0.0 %, 0.712
Mutual adjustment for maternal and paternal age	2	0.85 (0.64–1.12)	0.0 %, 0.482	2	0.63 (0.33–1.20)	0.0 %, 0.448	2	1.07 (0.95–1.21)	0.0 %, 0.341
Subgroups by overall study quality									
Low (NOS 1–3)	0	No studies		0	No studies		0	No studies	
Intermediate (NOS 4–6)	7	1.03 (0.87–1.24)	0.0 %, 0.449	7	**1.54 (1.12–2.10)**	47.9 %, 0.074	0	No studies	
High (NOS 7–9)	9	1.11 (0.80–1.55)	58.2 %, 0.014	8	1.07 (0.82–1.38)	5.4 %, 0.389	7	1.04 (0.98–1.09)	31.7 %, 0.186
Sensitivity analyses about older age									
Sensitivity analysis, with cut-off set at 35 years	15	1.06 (0.87–1.30)	43.0 %, 0.039		Not applicable			Not applicable	
Sensitivity analysis, with cut-off set at 40 years	3	1.44 (0.89–2.34)	0.0 %, 0.372		Not applicable			Not applicable	
Sensitivity analysis about younger age									
Sensitivity analysis, with cut-off set at 20 years		Not applicable		3	1.05 (0.40–2.78)	48.0 %, 0.146		Not applicable	

Bold cells denote statistically significant associations

[a] Number of study arms

case–control studies included the lack of adjusted effect estimates, the self-reported parental age, as well as the inclusion of hospital-based controls. The quality of cohort studies was often compromised by unadjusted effect estimates; on the other hand, the length of follow-up was satisfactory, as a rule.

Supplemental Table 3 presents the results of meta-regression analysis. No modifying effects mediated by publication year or mean age of study subjects were observed. Larger percentage of male offspring in the individual studies was associated with 1.5-fold increased RRs for mixed leukemia at the analysis pertaining to oldest mothers (exponentiated coefficient = 1.45, 95 % CI 1.02–2.05) and 1.8-fold increased RRs for AML at the analysis concerning youngest fathers (exponentiated coefficient = 1.85, 95 % CI 1.02–3.35).

The results of Egger's test are presented in Supplemental Table 4; no evidence of publication bias was documented in any analysis.

Discussion

This meta-analysis, based on a considerable number of study subjects and a well-defined exposure variable, presents a compendium of novel messages regarding the role

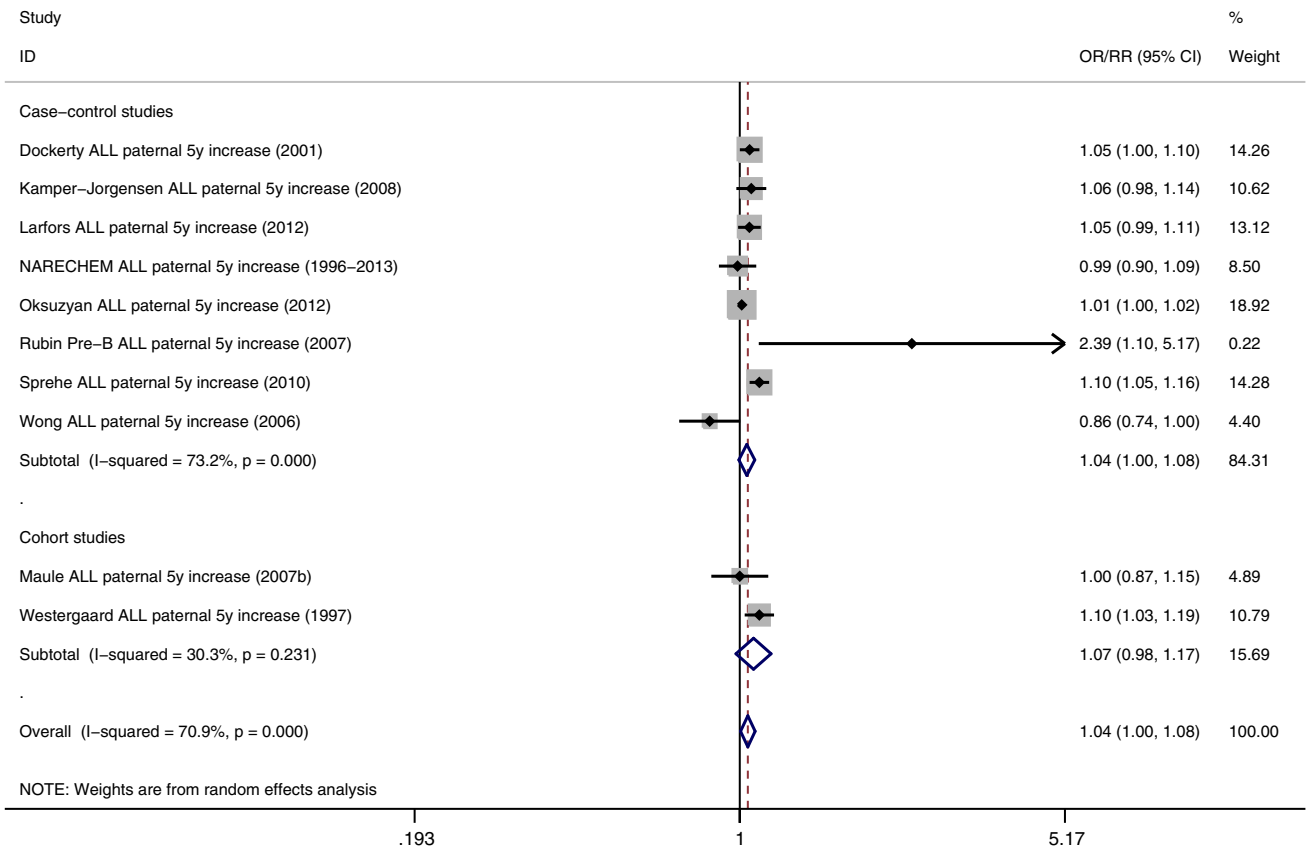

Fig. 3 Forest plot describing the association between risk for childhood ALL and paternal age (incremental analysis). Apart from the overall analysis, the sub-analyses on case–control (*upper panels*) and cohort (*lower panels*) studies are presented

of parental age in the epidemiology of childhood leukemia. Older maternal age was found to be associated with 5 % increased risk for childhood ALL in the offspring for every 5-year increase in maternal age; this was reflected among the oldest maternal age categories across all included studies, which presented with 10 % increased risk for childhood ALL compared to the averagely-aged mothers. On the other hand, maternal age was associated with risk of childhood AML in a U-shaped manner, as both oldest and youngest extremes were symmetrically associated with 23 % increased risk for AML; consistently, in view of the underlying, strikingly symmetric pattern, the incremental analysis yielded a null result.

Apart from the mother, this meta-analysis also brings to the foreground the role of fathers in the epidemiology of childhood leukemia. Although the roles of maternal and paternal age cannot be easily disentangled, as they are often be closely associated with each other, the meta-analysis yielded evidence that older paternal age correlated with increased risk for childhood ALL in the offspring, with 4 % increased risk observed for every 5-year increase in paternal age. Interestingly, younger fathers seemed at 28 % increased risk of having a child with childhood AML compared to their average-aged counterparts; the respective association with ALL was substantially milder, therefore not being able to neutralize the overall incremental pattern.

Regarding older parental age, the underlying mechanisms seem to entail a genetic component, given that older parental age could theoretically lead to increased risk for childhood leukemia in view of genetic hits accumulating in the germ cells [24]. Apart from this traditionally anticipated association applying to both parents, the increased risk for leukemias (AML and, to a lesser extent, ALL) noted among the offspring of younger fathers seems considerably more intriguing. Strikingly, a recently published study highlighted elevated germline mutation rates in teenage fathers, with the sperm cells of adolescent boys having more than six times the rate of DNA mutations as the equivalent egg cells in adolescent girls, a fact that may result in higher rates of DNA mutations being passed down to children of teenage fathers [25]. Apart from the genetic factor, the lower socioeconomic and educational status of the youngest parents [26] may underlie the observed associations; a broader analogy emerges, as studies in various fields have documented increased morbidity among

children stemming from younger parents [27]. Lower socioeconomic status in teenaged parenthood may also signal the presence of numerous coexistent potential risk factors, such as parental smoking [28] or alcohol consumption, that are often intercorrelated and socially patterned [29]. Furthermore, it should be kept in mind that this finding was mainly based on case–control studies; recruitment of young father controls may have been historically difficult due to limited phone access or high mobility, hence the results should be interpreted with caution.

As our eligible studies span nearly six decades and researchers have supported the importance of temporal trends along birth cohorts [30], it seemed of special importance to perform a meta-regression analysis, which suggested, however that publication year did not modify the observed associations. Moreover, the observed associations were not modified by the mean age of participants. On the other hand, male offspring seemed occasionally more burdened by the effects of parental age; the underlying mechanisms for this observation remain unknown. It seems worth noting nevertheless that meta-analyses on the detrimental effects of parental age on other conditions, such as schizophrenia [31] and autism [32], have pointed to special vulnerability of male versus female offspring.

Apart from pooling data to arrive to a meta-estimate, this study served the effort to address heterogeneity in the published data. Regarding oldest and youngest maternal age, heterogeneity was moderate for ALL but impressively small for AML; moderate heterogeneity was noted for father's age at the respective analyses, as a rule. On the other hand, incremental analyses presented with substantial heterogeneity for ALL in both maternal and paternal age, whereas the respective measures were only indicative of moderate heterogeneity for AML; notably, in all major analyses, I^2 value was <75 % [22]. As evident in the conducted subgroup analyses and meta-regression analyses, sources of heterogeneity included study design, geographic regions reflecting genetic factors as well as sociocultural aspects pertaining to the reproductive age, the overall study quality and especially adjustment factors, as well as the degree of representation of male children in the studies. On the other hand, period effects (assessed through publication year) did not seem to play a major role.

From a methodological point of view, this meta-analysis highlights many features and shortcomings of the existing literature, opening the way to future studies. Numerous studies presented unadjusted effect estimates; moreover, among those which presented adjusted relative risks, only a small subset proceeded to a mutual adjustment between maternal and paternal age. Nevertheless, in view of the present findings, which equally recognize the importance of the maternal and paternal factor, it seems desirable to envisage future studies discriminating between the two effects in terms of elaborate adjusting, taking always care of the potential collinearity that these factors may present. At this point, the limitation of the meta-analysis approach as a research tool versus the pooled analysis of individual data should be acknowledged; consortia with individual family data on both maternal and paternal age seem to be needed for the optimal evaluation of this research question. Regarding the external generalizability of findings, it seems worth underlining that the majority of studies came from Europe and North America; Asia, Latin America were underrepresented, whereas there was a lack of data concerning Africa.

Further on, it seems desirable that future studies proceed to meticulous analyses, presenting both incremental and categorical approaches. On one hand, given the U-shaped association in AML, a purely incremental analysis seems inadequate. On the other hand, incremental analyses provide a straightforward, uniform way to quantify the effect of exposure; in our meta-analyses, only a subset of studies approached the phenomenon incrementally and therefore the study numbers in incremental analyses were considerably smaller than the respective categorical ones. Moreover, wherever possible given the sample size, extreme age subgroups should also be examined; in our approach, sensitivity analyses focusing on the extremes of <20 and >40 years of age were undertaken in an attempt to explore dose–response patterns, but were essentially hampered by the small number of eligible study arms. Separate reporting by ALL and AML seems a minimum recommendation, given that admixture of cases in studies examining total leukemia does not allow the emergence of clear patterns, as highlighted by our Supplementary analysis. In addition, future studies should ideally aim to report results by immunophenotype or genetic subgroups, to allow the testing of underlying mechanisms on a genetic basis.

Despite the aforementioned notions pertaining to the methodology of constituent eligible studies, the meta-analysis bears certain strengths, among which the large number of studies and study subjects, the lack of publication bias, as well as the fact that cohort and case–control studies pointed to the same direction, as a rule. Nevertheless, additional data derived from cohort studies seem desirable, as the majority of data came from case–control studies, which are inherently prone to biases [33]. Finally, in our subgrouping strategy, we did not further subdivide on the basis of geography, degree of adjustment or overall quality, separately in the case–control and cohort subsets, in view of the emerging small numbers of study arms that would render the effect estimates unstable.

In conclusion, this meta-analysis portrays maternal as well as paternal age as meaningful risk factors for

childhood leukemias. ALL and AML may well follow distinct patterns in their associations with parental age. Further, well-adjusted studies, eventually coming from large consortia, are anticipated to address methodological issues satisfactorily, whereas the potential underlying genetic mechanisms should be elucidated by basic research studies.

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