Parental infertility and offspring cardiometabolic trajectories: a pooled analysis of three European cohorts

Álvaro Hernáez, D.Pharm., Ph.D.,[a,b,c] Ahmed Elhakeem, Ph.D.,[d,e] Henrique Barros, M.D., Ph.D.,[f,g] Tanja G. M. Vrijkotte, Ph.D.,[h] Abigail Fraser, Ph.D.,[d,e] Deborah A. Lawlor, M.D., Ph.D.,[d,e,i] and Maria C. Magnus, Ph.D.[a]

[a] Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway; [b] Blanquerna School of Health Sciences, Universitat Ramon Llull, Barcelona, Spain; [c] Consorcio CIBER, M.P. Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain; [d] MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, United Kingdom; [e] Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom; [f] EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal; [g] Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional, Porto, Portugal; [h] Department of Public and Occupational Health, Amsterdam Public Health Research Institute, Amsterdam Reproduction and Development Research Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; and [i] National Institute for Health Research Bristol Biomedical Research Centre, Bristol, United Kingdom

Objective: To assess whether parental infertility is associated with differences in cardiometabolic trajectories in offspring.
Design: Pooled observational analysis in three prospective cohorts.
Setting: Three nationwide pregnancy cohorts.
Patients: A total of 14,609 singletons from the UK Avon Longitudinal Study of Parents and Children, the Portuguese Geraçao 21, and the Amsterdam Born Children and Their Development study. Each cohort contributed data up to ages 26, 12, and 13 years, respectively.
Intervention: Parental infertility is defined as time-to-pregnancy of $\geq$12 months (n = 1,392, 9.5%).
Main Outcome Measures: Trajectories of body mass index (BMI), waist circumference, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C) level, high-density lipoprotein cholesterol (HDL-C) level, triglycerides level, and glucose level were compared in the offspring of couples with and without infertility. Trajectories were modeled using mixed-effects models with natural cubic splines adjusting for cohort, sex of the offspring, and maternal factors (age, BMI, smoking, educational level, parity, and ethnicity). Predicted levels of cardiometabolic traits up to 25 years of age were compared with parental infertility.
Results: Offspring of couples with infertility had increasingly higher BMI (difference in mean predicted levels by age 25 years: 1.09 kg/m2, 95% confidence interval [0.68–1.50]) and suggestively higher diastolic blood pressure at age 25 years (1.21 mmHg [−0.003 to 2.43]).

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The consent given by the participants does not allow individual-level participant data to be presented in repositories or journals. Data used in this study are available to bone fide researchers on request to each cohort (ALSPAC: application to the ALSPAC Executive Committee through https://proposals.epi.bristol.ac.uk/; G21: application to Dr. Henrique Barros, henrique.barros@ispup.up.pt; ABCD: application according to the guidelines in the ABCD website [https://www.amc.nl/web/abcd-studie-2/abcd-studie/achtergrondinformatie-abcd-studie.htm], directed to abcd@amsterdamumc.nl). Please contact Prof. Deborah A. Lawlor (d.a.lawlor@bristol.ac.uk) and Dr. Ahmed Elhakeem (a.elhakeem@bristol.ac.uk) if you have relevant data and would like to join the A.R.T.-HEALTH partnership (https://arthealth.bristol.ac.uk/) and contribute to future collaborations.
Correspondence: Álvaro Hernáez, D.Pharm., Ph.D., Centre for Fertility and Health, Norwegian Institute of Public Health, PO 222 Skøyen, Oslo 0213, Norway (E-mail: alvaro.hernaez@fhi.no).

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Their LDL-C tended to be higher, and their HDL-C values tended to be lower over time (age: 25 years, LDL-C: 4.07% [−0.79 to 8.93]; HDL-C: −2.78% [−6.99 to 1.43]). At age 17 years, offspring of couples with infertility had higher waist circumference (1.05 cm [0.11–1.99]) and systolic blood pressure (age: 17 years; 0.93 mmHg [0.044–1.81]), but these differences attenuated at later ages. No intergroup differences in triglyceride and glucose level trajectories were observed. Further adjustment for paternal age, BMI, smoking, and educational level, and both parents' histories of diabetes and hypertension in the cohort with this information available (Avon Longitudinal Study of Parents and Children) did not attenuate intergroup differences.

Conclusion: Offspring of couples with infertility relative to those of fertile couples have increasingly higher BMI over the years, suggestively higher blood pressure levels, and tend to have greater values of LDL-C and lower values of HDL-C with age. (Fertil Steril® 2024;121:853–63. ©2024 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Infertility, offspring, cardiometabolic, trajectories, ALSPAC

Individuals reporting fertility problems develop more cardiovascular disease (1–6). Women with infertility have higher body mass index (BMI), waist circumference (WC), and triglyceride (TG) levels, greater odds of diabetes, and lower concentrations of high-density lipoprotein cholesterol (HDL-C) compared with fertile women (7), whereas men with infertility are more likely to be obese and hypertensive (8). More adverse cardiometabolic health could be also present in their offspring. First, cardiometabolic disease and its risk factors are inheritable (9). Second, infertility is linked to pregnancy complications such as gestational diabetes (10) and hypertensive disorders of pregnancy (11), which are associated with increased cardiometabolic risk in the offspring (12, 13). Third, couples with fertility problems are likely to use assisted reproductive technology (ART) treatments, which are related to differences in cardiometabolic trajectories in their offspring in relation to those of fertile couples (14, 15). We previously reported that ART-conceived offspring, relative to fertile controls, had a lower BMI, WC, systolic blood pressure (SBP), and diastolic blood pressure (DBP), respectively, in childhood, and subtle trajectories to higher SBP and TG levels in young adulthood, although these differences were small (14, 15). Only three other studies to date have examined cardiometabolic risk factors in the offspring of individuals with infertility (16–18), most focused on changes in BMI, and reported minimal or null differences between the offspring of couples with and without infertility. Whether differences in cardiometabolic trajectories of offspring conceived using ART treatment are because of the ART procedures or underlying parental infertility remains unclear.

Our study therefore aims to determine the association of parental infertility (not considering ART use) with offspring trajectories of BMI, WC, SBP, DBP, LDL-C level, HDL-C level, TG level, and glucose level from birth to adulthood.

MATERIALS AND METHODS

Population Description

Our analyses are part of the Assisted Reproductive Technology and Health (A.R.T.-HEALTH) partnership (14, 15). All cohorts in the partnership were invited to participate in this study, with the inclusion criteria being that they had information on time-to-pregnancy for that specific pregnancy and two or more measurements taken at different times for at least one of the eight cardiometabolic traits of interest. Three cohorts fulfilled these requirements: the UK Avon Longitudinal Study of Parents and Children (ALSPAC; birth years: 1990–1992) (19–23), the Portuguese Geraçao 21 (G21; birth years: 2000–2006) (24), and the Dutch Amsterdam Born Children and their Development Study (ABCD; birth years: 2003–2004) (25). A detailed description of the number of mothers, partners, pregnancies, and offspring included in the ALSPAC study is available in the Supplemental Methods (available online). In the ALSPAC study, data were collected and managed using Research Electronic Data Capture electronic data capture tools hosted at the University of Bristol (26). The ALSPAC study website (http://www.bristol.ac.uk/alspac/researchers/our-data/) contains details of all the data that are available through a searchable data dictionary and variable search tool.

Figure 1 shows the flow chart of the study. Our analyses are considered singletons only and are reported following the guidelines described by the Strengthening the Reporting of Observational Studies in Epidemiology Statement.

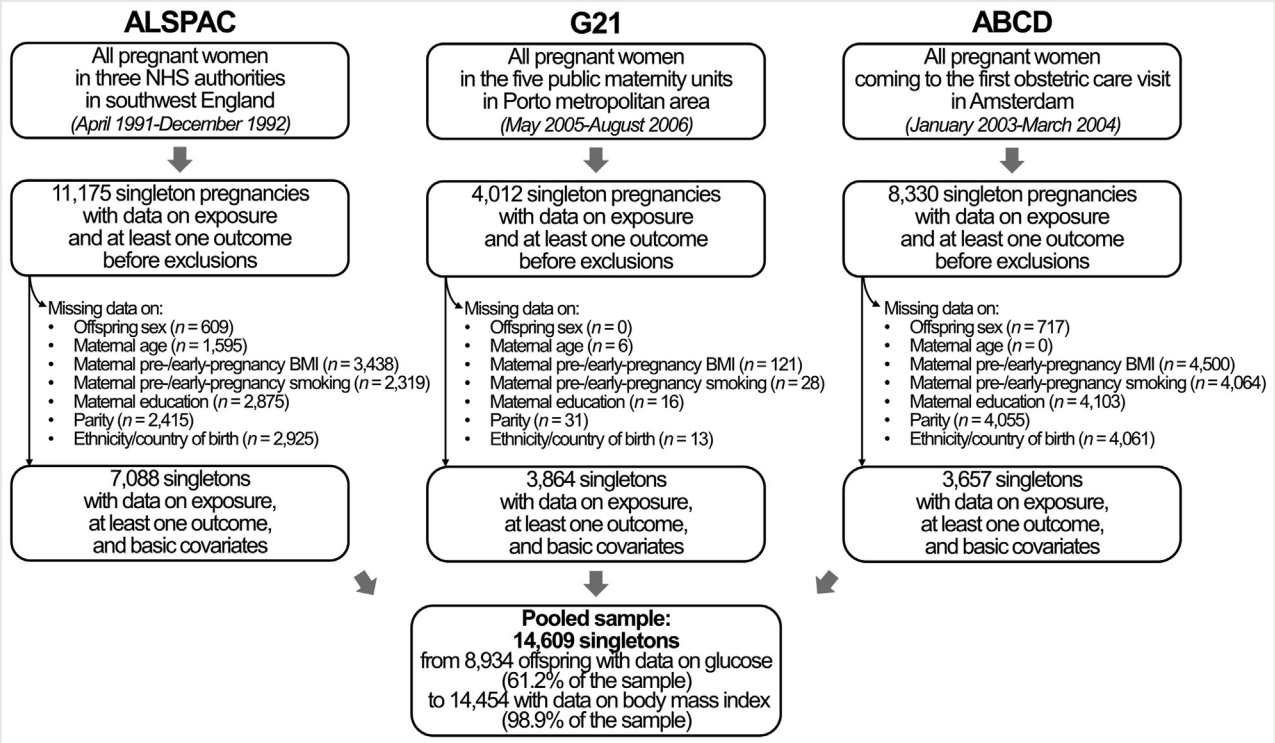
Infertility

Infertility is defined, in accordance with the World Health Organization, as a time-to-pregnancy of >12 months (27). Offspring of couples reporting a time-to-pregnancy of ≤12 months ("fertile") were included in the reference group. Unplanned pregnancies were included in the reference group. Offspring conceived using ART therapy in couples reporting a time-to-pregnancy of ≤2 months (n = 689) were excluded from the analyses.

Cardiometabolic Risk Factors in the Offspring

In 23 visits, the ALSPAC study collected data on BMI (median number of measures: 10 [interquartile range {IQR 9}]; age range: 0–26 years), WC (median: 7 measures [IQR 4]; 2–26 years), blood pressure (median: 7 measures [IQR 4]; 3–26 years), lipid profile (median: 2 measures [IQR 3]; 3–26 years), and glucose (median: 2 measures [IQR 2]; 7–26 years). Over the course of 45 visits, G21 collected data on BMI (median: 18 measures [IQR 9]; 0–12 years) and the rest of the risk factors (up to 3 measures; 3–12 years). Over 26 visits, ABCD collected data on BMI (median: 11 measures [IQR 4]; 0–12 years) and the rest of the risk factors (up to 2 measures; 5–13 years). The combined dataset had repeated measures of

FIGURE 1



Flow chart of the study.

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BMI (median: 12 measures [IQR 7]), WC (median: 3 measures [IQR 4]), blood pressure (median: 3 measures [IQR 5]), lipid profile (median: 2 measures [IQR 2]), and glucose (median: 2 measures [IQR 1]).

In the ALSPAC study, height and weight come from parental questionnaires (before age 16 years), self-measurements (after age 16 years), health records, school records, or research clinics, whereas WC circumference is measured to the nearest millimeter at research clinics. In the G21 study, anthropometric data were obtained by trained examiners. In the ABCD study, anthropometric information came from the youth health care registration of the Public Health Service in Amsterdam (by trained nurses) or research clinics. Blood pressure was measured at rest with validated sphygmomanometers (ALSPAC: average of two measurements; G21: average of two measurements when the difference between them was <5 mmHg [when greater, a third measurement was conducted and the mean of the two closest ones was calculated]; ABCD: average of two measurements). Regarding the biochemical determinations, in the ALSPAC study, lipids were measured using standard laboratory tests (following the standard Lipid Research Clinics Protocol, using enzymatic reagents) in nonfasting plasma or serum up to age 9 years and in fasting samples for older ages, and glucose was quantified in nonfasting venous blood samples using nuclear magnetic resonance at age 7 years and using standard laboratory tests in fasting samples at older ages (as above). In the G21 study, lipids and glucose levels were assessed in fasting venous blood samples (lipids: enzymatic colorimetric assays; glucose: hexokinase method). In the ABCD study, lipids and glucose were measured using a validated ambulatory collection kit on fasting capillary blood samples (Demecal: Lab Anywhere, Haarlem, the Netherlands). The LDL-C level was calculated using the Friedewald formula (LDL-C = total cholesterol − HDL-C − [TG/5]).

Confounders

Before analyses, we defined confounders as known and plausible causes of parental infertility and offspring cardiometabolic traits: parental age, socioeconomic position (education as a proxy), ethnicity, parity, and the number of children, as well as prepregnancy and early-pregnancy cardiometabolic risk factors of the parents (BMI, smoking, hypertension, and diabetes) (14, 15). Because some were assessed during pregnancy, we assumed a strong correlation between prepregnancy and during-pregnancy measures. Because we pooled individual participant data into one database, we only included confounders that were available in all studies and harmonized them to the lowest common denominator (14, 15). These were maternal age at pregnancy and birth (years, continuous), prepregnancy or early-pregnancy

maternal BMI (kg/m^2, continuous), prepregnancy or early-pregnancy maternal smoking (yes or no), maternal educational level (medium-high level or low level; medium-high education level was defined as 13+ years [ALSPAC], 10+ years [G21], and 14+ years of schooling [ABCD], whereas low education level was defined as any shorter duration of schooling), parity (0 or 1 or more), and ethnicity or country of birth [European or other]). We also adjusted for offspring sex to improve estimate precision. The ALSPAC study had further information on paternal prepregnancy age (continuous), early-pregnancy BMI (continuous), history of smoking (yes or no), educational level (medium-high level or low level, as described above), and both parents' histories of diabetes and hypertension (yes or no).

Ethics

All cohorts comply with the Declaration of Helsinki for medical research involving human subjects. In all three studies, informed written consent for the collection and use of data was provided by parents up to offspring age 16, 12, and 13 years (in ALSPAC, G21, and ABCD, respectively) and thereafter by the offspring in ALSPAC. In the ALSPAC study, ethical approval is provided by the ALSPAC Ethics and Law Committee and UK Local Research Ethics Committees (http://www.bristol.ac.uk/alspac/researchers/research-ethics/), consent for biologic samples was collected following the Human Tissue Act (2004), and informed consent for the use of data collected using questionnaires and clinics was obtained following the recommendations of the ALSPAC Ethics and Law Committee at the time. In the G21 study, ethical approval is provided by the Ethics Committee of Hospital de São João and the Institute of Public Health of the University of Porto. In the ABCD study, it is provided by the Netherlands Central Committee on Research involving Human Subjects, the Medical Ethical Committees of the participating hospitals, and the Registration Committee of the Municipality of Amsterdam.

Statistical Analyses

We described normally distributed variables with means and SDs and categorical variables with proportions. Differences in baseline characteristics of participants included and not included in our analyses were studied using *t*-tests and χ^2 tests for normally distributed continuous variables and categorical variables, respectively.

Individual participant data were merged and analyzed together. We assessed the association of parental infertility with offspring age-related cardiometabolic trajectories using mixed-effects linear regression with natural cubic splines (28). We used a natural cubic spline function for age as a fixed effect to model the cardiometabolic health trajectories, which allowed for the detection of nonlinear changes in outcomes with age. Models included seven knots for BMI, five for WC, three for SBP and DBP, two for lipid profile measures, and one for glucose (14, 15). Knots were placed at equal quantiles of age. Each cohort contributed data for different age ranges (ALSPAC up to age 26 years, G21 up to age 12 years, and ABCD up to age 13 years). The main analyses were adjusted for cohort, offspring sex, maternal age, maternal BMI, maternal smoking, maternal educational level, parity, and ethnicity, and included an interaction term between age at cardiometabolic measurements and parental infertility to allow for different trajectories in offspring born of couples with infertility and those without. We used predicted values to plot mean trajectories in both populations and used them to calculate the mean differences in cardiometabolic factors between ages 1 and 25 years every 2 years. Differences in the measured values are presented for BMI, WC, SBP, and DBP. The LDL-C, HDL-C, triglycerides, and glucose levels were log-transformed before analysis, and the intergroup differences presented are the percent difference between the exposure groups. Participants with missing covariates were excluded from the analyses.

Because we were unable to adjust for all a priori defined confounders in the main analyses, in the subsample of ALSPAC study participants with available data on the confounders in the main analyses plus the additional confounders (paternal age, BMI, smoking, and educational level, and both parent's history of diabetes and hypertension, n = 3,847), we compared the analyses adjusted for the covariates available in all three cohorts and those adjusted for all the confounders. Besides, we conducted three sensitivity analyses. First, to check the consistency of trajectories across cohorts, we conducted trajectory analyses in ALSPAC, G21, and ABCD studies separately and compared their shapes by visual inspection. Second, to check the assumption that the results are from the same underlying population, we limited our analyses to the age range for which there is information in the three cohorts (ages 1–15 years for BMI, ages 5–11 years for the other outcomes) and compared their shapes with the main results using visual inspection. Finally, to check whether our results were consistent with a broader definition of infertility (time-to-pregnancy > 12 months + ART use), we repeated the analyses using the definition for the exposure that also included offsprings conceived through ART treatments. All analyses were performed in R Software version 4.0.3.

RESULTS

Study Population

We studied 14,609 singleton offspring, of whom 1,392 (9.5%) were born to couples with infertility. The main analyses were conducted on the following exact numbers of offspring: 14,454 for BMI, 11,565 for WC, 11,443 for blood pressure, 9,343 for lipid profile, and 8,934 for glucose levels. In couples experiencing infertility, the mothers were older, had a slightly higher BMI, smoked more frequently, had lower levels of education, had fewer previous pregnancies, and were more likely to be of non-European origin (Table 1).

Maternal age at birth, BMI, and smoking were similar across cohorts. Nevertheless, low maternal education and high parity were more frequent in the ALSPAC study, and a higher proportion of participants of non-European origin was observed in the ABCD (Supplemental Table 1, available online). Parents of nonincluded offspring were younger,

TABLE 1

Population description.

Description	Couples with infertility (n = 1,392)	Fertile couples (n = 13,217)
Cohort		
ALSPAC, n (%)	652 (46.8)	6,436 (48.7)
G21, n (%)	368 (26.4)	3,496 (26.5)
ABCD, n (%)	372 (26.7)	3,285 (24.9)
Sex of offspring		
Female, n (%)	690 (49.5)	6,536 (49.5)
Male, n (%)	702 (50.5)	6,681 (50.5)
Maternal age at birth or pregnancy, mean ± SD	31.0 ± 5.0	29.9 ± 4.5
Maternal prepregnancy body mass index, mean ± SD	24.2 ± 4.7	23.3 ± 3.8
Maternal prepregnancy smoking:		
No, n (%)	1,062 (76.2)	10,643 (80.5)
Yes, n (%)	330 (23.8)	2,574 (19.5)
Maternal education		
Low, n (%)	799 (57.4)	6,189 (46.8)
Medium or high, n (%)	593 (42.6)	7,028 (53.2)
Maternal parity		
No previous births, n (%)	865 (62.1)	6,715 (50.8)
1 or more, n (%)	527 (37.9)	6,502 (49.2)
Maternal ethnicity or country of birth		
European, n (%)	1,209 (86.9)	12,045 (91.1)
Other, n (%)	183 (13.1)	1,172 (8.9)

Note: ABCD = the Dutch Amsterdam Born Children and their Development Study; ALSPAC = the UK Avon Longitudinal Study of Parents and Children; G21 = the Portuguese Geraçao 21.

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more likely to be smokers (in the ALSPAC and ABCD studies), less educated (in the ALSPAC and G21 studies), more likely to be of non-European origin, and more likely to have more than one offspring (in the G21 and ABCD studies) (Supplemental Table 2).

Adiposity Trajectories

In the adjusted analyses with pooled individual participant data, BMI differences emerged in childhood and increased with age (Fig. 2A). At age 25 years, offspring of couples with infertility had a higher mean BMI (1.09 kg/m^2, 95% CI: 0.68–1.50, Fig. 2B). Offspring of couples with infertility evolved to higher values of WC during adolescence (age: 17 years; 1.05 cm, 95% CI: 0.11–1.99), and these differences were attenuated in adulthood (Fig. 2C and D).

Blood Pressure

Offspring of couples with infertility had slightly higher mean SBP and DBP values (Fig. 2E and G). Intergroup differences for SBP peaked around late adolescence (age: 17 years; 0.93 mmHg, 95% CI: 0.04–1.81, Fig. 2F) and those of DBP in early adulthood (age: 25 years; 1.21 mmHg, 95% CI: −0.003 to 2.43, Fig. 2H).

Lipid Profile and Glucose

No clear associations between parental infertility, lipid profile, and glucose levels in the offspring were seen. Offspring of couples with infertility had lower average LDL-C during childhood (age: 5 years; −5.04%, 95% CI: −8.04 to 2.04); these differences disappeared by age 7 years and tended to increase over time from adolescence, which resulted in suggestively higher values in early adulthood (age: 25 years; 4.07%, 95% CI: −0.79 to 8.93, Fig. 3A and B). Offspring of couples with infertility also tended to have lower HDL-C levels, and this difference increased over time (age: 25 years; −2.78%, 95% CI: −6.99 to 1.43, Fig. 3C and D). Triglyceride level differences between offspring of couples with and without infertility were imprecise, with the largest difference seen during adolescence (age: 15 years; 3.09%, 95% CI: −1.24 to 7.42, Fig. 3E and F). Glucose levels in the offspring of infertile parents were only higher in childhood (age: 5 years; 1.00%, 95% CI: −0.16 to 2.16), but differences attenuated at later ages (Fig. 3G and H).

Additional Analyses

Further adjustment for the partner's confounders and both parents' histories of diabetes and hypertension in the ALSPAC study did not attenuate the intergroup differences in trajectories for any of the cardiometabolic traits (Supplemental Fig. 1, available online).

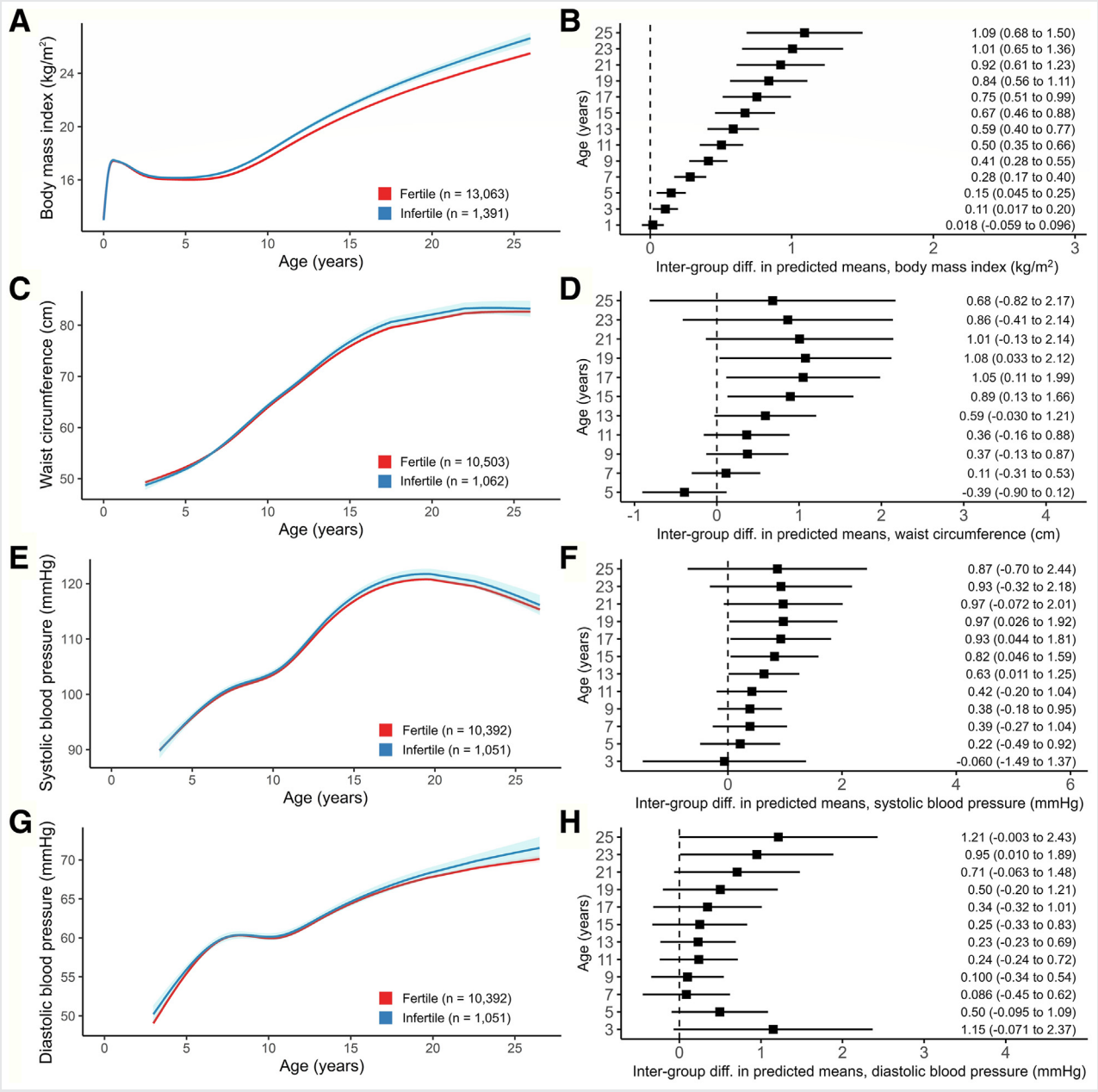
We observed no substantial differences in the cohort-specific trajectories for adiposity measures (Supplemental Fig. 2). We also observed no substantial differences in the cohort-specific trajectories for SBP. However, the DBP trajectories in the G21 study seemed different from what was observed in the other two cohorts. Nevertheless, intergroup differences in DBP in early adulthood in the main analyses were consistent with those observed for the ALSPAC study data only (Supplemental Fig. 3). We further observed no substantial differences in the cohort-specific trajectories for LDL-C and glucose levels (Supplemental Fig. 4A and D), but the shape of HDL-C and TG levels trajectories seemed not comparable across cohorts (Supplemental Fig. 4B and C).

Cardiometabolic trajectories in the age range for which there is information in the three cohorts were comparable for anthropometric measures, blood pressure, and LDL-C levels, but not for HDL-C, TG, and glucose levels (Supplemental Fig. 5). Including ART treatment in the definition of infertility slightly attenuated the differences in BMI between the offspring of couples with infertility and those without, but it did not notably change the rest of the results (Supplemental Fig. 6).

DISCUSSION

We found that offspring of couples with infertility had higher BMI from childhood to adulthood (differences widened with age and reached their maximum at 25 years, with a difference of 1.1 kg/m^2), higher WC during adolescence (these

FIGURE 2



Trajectories of cardiometabolic traits from birth to early adulthood in offspring of couples with (blue) and without infertility (red) and differences in mean predicted values for body mass index (**A** and **B**), waist circumference (**C** and **D**), systolic blood pressure (**E** and **F**), and diastolic blood pressure (**G** and **H**).

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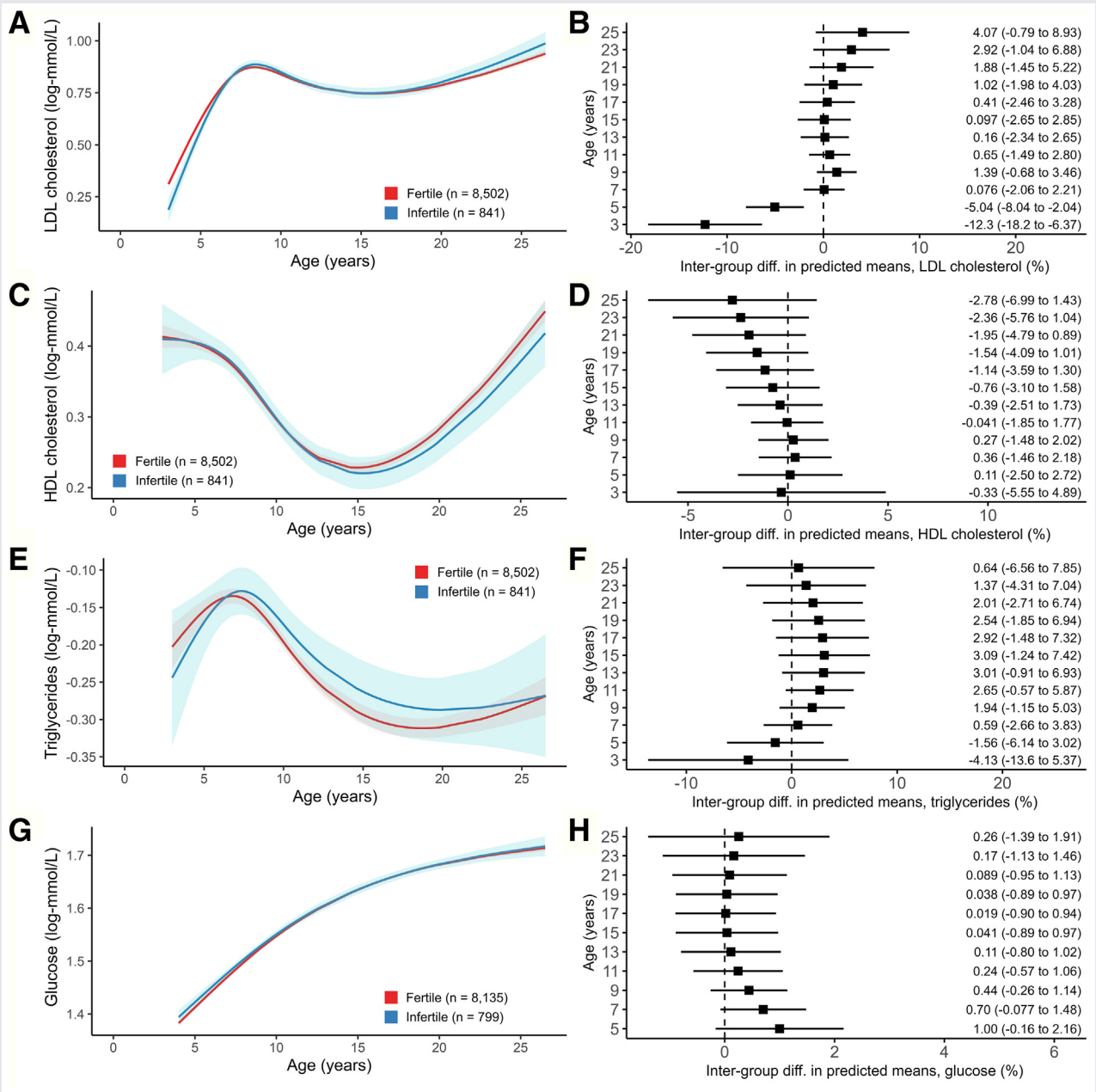
differences attenuated in later ages), slightly higher mean SBP and DBP from childhood to adulthood, and tended to have higher LDL-C levels and lower HDL-C levels in adulthood (these trends emerged in adolescence and broadened over time). The observed differences were robust to adjustment, including for parental risk factors for cardiovascular disease and infertility.

There is limited evidence available on differences in cardiometabolic health according to parental infertility. In a previous study of 4,151 Danish singletons with 1–28 measures of weight between ages 0–20 years, offspring of couples with infertility showed a greater linear increase in weight per year until age 10 years (16). Two other studies (one with 1,773 Danish children with one BMI measurement at age 5 years and one with 79,740 Norwegian children with 12 BMI measurements between ages 0 and 7 years) reported no association between parental infertility and offspring BMI (17, 18), which is consistent with our findings of no differences up to

FIGURE 3



Trajectories of cardiometabolic traits from birth to early adulthood in offspring of couples with (blue) and without infertility (red) and differences in mean predicted values for low-density lipoprotein (LDL) cholesterol (**A** and **B**), high-density lipoprotein (HDL) cholesterol (**C** and **D**), triglycerides (**E** and **F**), and (**G** and **H**).

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age 7 years. We did not find more studies on the topic that did not involve participants from the ALSPAC, G21, or ABCD studies (the only other study available is based on the ABCD study data) (29). A 1 kg/m^2 greater BMI value in the offspring of couples with infertility at age 25 years, potentially growing larger when trends in our data persist, has been associated with increased risk of metabolic syndrome even in middle adulthood (30) and more risk of chronic disease and all-cause mortality at later ages, particularly in individuals with BMI values over 25 kg/m^2 (31). In contrast, variations in other risk factors were modest and might have more limited clinical significance.

Previous bibliographies have focused on differences in cardiometabolic health according to conception using ART treatment. The work presented here builds on two previous articles of ours in which we explored the association of

ART conception with cardiometabolic traits, cross-sectionally at different ages from infancy to 26 years in all the A.R.T.-HEALTH partnership cohorts, and with cardiometabolic trajectories in a subgroup of the three cohorts included in this study plus a fourth cohort (GUSTO) (14, 15). In the cross-sectional analyses, ART-conceived offspring had slightly lower mean BMI and WC up to age 9 years compared with naturally conceived offspring, shifted toward higher adiposity values from age 17 years (15), and had higher LDL-C and HDL-C levels and no differences in blood pressure, TG levels, and glucose levels (14). In the trajectory analyses, ART-conceived offspring tended to have higher SBP and lower HDL-C levels over time and had higher glucose levels during the preschool years (14). Other studies have reported that ART-conceived offspring have lower BMI values under age 5 years (32) but a higher risk of obesity during later childhood and adolescence (33) and greater linear increments in weight until age 20 years (16). They also have lower blood pressure at the age of 6 years (32) and no increased risk of diabetes during childhood and adolescence (33). Overall, the findings of studies on ART-conceived offspring agree with our findings, showing a trend toward higher values of adiposity in adulthood, higher blood pressure, a trend toward lower HDL-C levels with age, and a lack of associations with glucose and TG levels. According to our results, underlying parental infertility might explain at least part of the differences in cardiometabolic health associated with ART use in previous publications of the A.R.T.-HEALTH partnership because differences remained when ART-conceived offspring were included in the exposed group of our analyses.

There are several potential explanations for the association between parental infertility and poorer cardiometabolic health in the offspring. Individuals with infertility are prone to having impaired cardiometabolic risk factors (7, 8), which may be inherited by their offspring (9). Infertility could be because of the underlying conditions in women, such as polycystic ovary syndrome, which is also linked to poorer cardiometabolic health in their offspring (34–36). In parallel, a shared detrimental environment (e.g., unhealthy diet and lack of physical activity) could explain both fertility problems in the parents and the differences in cardiometabolic health in the offspring (37, 38).

This work has some limitations. First, our exposure (parental infertility) is a couple-dependent measure, and we could not determine whether the fertility problems originated in the mothers, their male partners, or both. Second, regarding confounding, we a priori acknowledged known and plausible causes of parental infertility, offspring cardiometabolic traits, and several sources of residual confounding. Some confounders were assessed during pregnancy (after the exposure), and we had to assume that there was a strong correlation between prepregnancy and during-pregnancy measures. Results in the ALSPAC study adjusting for confounders available in all three cohorts were not different from those after adjusting for the common covariates plus paternal education, smoking, BMI, and paternal and maternal hypertension and diabetes. Residual confounding by paternal dyslipidemia may explain some of the associations, particularly those with offspring lipids, because this variable was unavailable. The harmonization of confounders to the lowest common denominator may have also resulted in additional residual confounding. Third, our study involves differential age ranges in our cardiometabolic trait data across the three cohorts. For the G21 and ABCD studies, data are limited to ages 3–12 years, whereas the ALSPAC study extends up to the age of 26 years. Consequently, our findings regarding cardiometabolic trajectories from the age of 13–26 years are driven solely by the ALSPAC study. We assumed that the cardiometabolic trajectories for the three cohorts, given their shared European origin, would align. However, this assumption may not be entirely precise because there were inconsistencies in the trajectories within each cohort. In most cases, intercohort differences seem to be slightly more pronounced than those between the offspring of infertile and fertile couples. However, these discrepancies may be attributed to the limited number of data points for two of the cohorts, which may have affected the construction of polynomial equations and complicated a qualitative comparison between cohorts. We have also tried to minimize this source of bias by adjusting our analyses for cohort. In any case, our conclusions beyond 13 years of age may be subject to potential biases. They should be interpreted carefully and validated in further studies incorporating additional time points in adolescence, early adulthood, or later in life. Fourth, our results may have been also affected by selection bias because there were some differences between included and nonincluded participants (included participants were older, less likely to be smokers, more educated, more likely to be of European origin, and less likely to have more than one offspring). Fifth, the ALSPAC study measured lipids in nonfasting plasma or serum samples up to the age of 9 years and glucose in nonfasting venous blood samples at the age of 7 years. In contrast, the remaining measurements in this cohort and the other two were conducted using fasting blood, plasma or serum samples. This difference in sample collection methods may have contributed to the variability of these parameters among the three cohorts within this age range, potentially limiting our ability to detect differences. Finally, our study population, primarily of European origin, may limit the generalizability of our findings to populations with similar genetic backgrounds.

CONCLUSIONS

Offspring of couples with infertility, compared with those of fertile couples, had increasing BMI differences over time, higher WC in adolescence (which was later attenuated), slightly higher blood pressure from childhood to adulthood, and tended to have higher LDL-C levels and lower HDL-C levels with age (starting in their adolescence). To our knowledge, this is the largest study assessing the differences in cardiometabolic trajectories between birth and early adulthood according to parental infertility. These findings require validation in larger cohorts, measures at older ages, and a better understanding of their mechanisms, but they suggest that parental infertility may be an indicator of a poorer cardiometabolic profile in offspring.

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CRediT Authorship Contribution Statement

Álvaro Hernáez: Writing – original draft, Visualization. **Ahmed Elhakeem:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Henrique Barros:** Writing – review & editing, Resources, Data curation. **Tanja G.M. Vrijkotte:** Writing – review & editing, Resources, Data curation. **Abigail Fraser:** Writing – review & editing, Supervision. **Deborah A. Lawlor:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Maria C. Magnus:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of interests

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Infertilidad parental y trayectorias cardiometabólicas de la descendencia: análisis conjunto de tres cohortes europeas.

Objetivo: Evaluar si la infertilidad parental se asocia con diferencias en el comportamiento cardiometabólico en la descendencia.

Diseño: Análisis observacional agrupado en tres cohortes prospectivas.

Entorno: Tres cohortes de embarazos de ámbito nacional.

Pacientes: Un total de 14.609 hijos únicos del Estudio Longitudinal Avon de Padres e Hijos del Reino Unido, del estudio portugués Geracao 21, y
del estudio Amsterdam Born Children and Their Development. Cada cohorte aportó datos hasta los 26, 12 y 13 años de edad, respectivamente.

Intervención: La infertilidad parental se define como un tiempo hasta el embarazo de R12 meses (n . 1.392, 9,5%).

Principales medidas de resultados: Se compararon las evoluciones del índice de masa corporal (IMC), el perímetro de cintura, la presión arterial sistólica, la presión arterial diastólica, el nivel de colesterol de lipoproteínas de baja densidad (LDL-C), el nivel de colesterol de lipoproteínas de alta densidad (HDL-C), el nivel de triglicéridos y el nivel de glucosa en la descendencia de parejas con y sin infertilidad. Las evoluciones se modelaron mediante modelos de efectos mixtos con splines cúbicos naturales ajustados por cohorte, sexo de la descendencia y factores maternos (edad, IMC, tabaquismo, nivel educativo, paridad y etnia). Los niveles predichos de rasgos cardiometabólicos hasta los 25 años de edad se compararon con la infertilidad parental.

Resultados: Los hijos de parejas con infertilidad tenían un IMC cada vez más elevado (diferencia en los niveles medios previstos a los 25 años: 1,09 kg/m2, intervalo de confianza del 95% [0,68-1,50]) y una presión arterial diastólica sugestivamente más alta a la edad de 25 años (1,21 mmHg [0,003 a 2,43]). Sus valores de LDL-C tendían a ser más altos, y sus valores de HDL-C tendían a ser más bajos con el tiempo (edad: 25 años, LDL-C: 4,07% [0,79 a 8,93];HDL-C: 2,78% [6,99 a 1,43]). A los 17 años, los hijos de parejas con infertilidad tenían un perímetro de cintura (1,05 cm [0,11-1,99]) y una presión arterial sistólica (edad: 17 años; 0,93 mmHg [0,044-1,81]) más elevados, pero estas diferencias se atenuaron a edades más avanzadas. No se observaron diferencias intergrupales en las evolucioness de los niveles de triglicéridos y glucosa. Los ajustes adicionales por edad paterna, IMC, tabaquismo y nivel educativo, así como los antecedentes de diabetes e hipertensión de ambos progenitores en la cohorte que disponía de esta información (Avon Longitudinal Study of Parents and Children) no atenuaron las diferencias intergrupales.

Conclusiones: Los hijos de parejas con infertilidad en relación con los de parejas fértiles tienen un IMC cada vez más elevado con los años, niveles de presión arterial sugestivamente más altos y tienden a tener valores mayores de LDL-C y menores de HDL-C con la edad.