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Abstract

Background: Do drinking patterns in late adolescence/early adulthood predict life-time childlessness and number of children? Research on this question has been only tangentially relevant and the results inconsistent. The designs used to date have been compromised by genetic and environmental confounds that are poorly controlled; covariate effects of smoking and education that are often ignored; males being understudied; population-based sampling rare, and long-term prospective studies with genetically informative designs yet to be reported.

Method: In a 33-year follow-up, we linked the drinking patterns of >3500 Finnish twin pairs, assessed at ages 18–25, to registry data on their eventual number of children. Analyses distinguished associations of early drinking patterns with lifetime childlessness from those predictive of family size. Within-twin pair analyses used fixed-effects regression models to account for shared familial confounds and genetic liabilities. Childlessness was analyzed with Cox proportional hazards models and family size with Poisson regression. Analyses within-pairs and of twins as individuals were run before and after adjustment for smoking and education, and for oral contraceptive (OC) use in individual-level analyses of female twins.

Results: Baseline abstinence and heavier drinking both significantly predicted lifetime childlessness in individual-level analyses. Few abstinent women used OCs, but they were nonetheless more often eventually childless; adjusting for smoking and education did not affect this finding. Excluding childless twins, Poisson models of family size showed heavier drinking at 18–25 to be predictive of fewer children in both men and women. Those associations were replicated in within-pair analyses of dizygotic twins, each level of heavier drinking being associated with smaller families. Among monozygotic twins, associations of drinking with completed family size yielded effects of similar magnitude, reaching significance at the highest levels of consumption, ruling out familial confounds.

Conclusions: Compared to moderate levels of drinking, both abstinence and heavier drinking in late adolescence/early adulthood predicted a greater likelihood of lifetime childlessness and eventual number of children. Familial confounds do not fully explain these associations.

INTRODUCTION

We investigated whether patterns of alcohol consumption in late adolescence and early adulthood predict lifetime childlessness and eventual number of biological children. We addressed that question with prospective study of a population-based Finnish twin sample. Previous research associating drinking patterns to measures of reproductive outcome have limited relevance for our research question. Research on reproductive success of women enrolled in fertility clinics has included self-reported alcohol use, along with that of tobacco and caffeine. But these studies are not prospective, vary widely in measures, samples, and design, and yield inconsistent evidence of drinking-outcome associations. Some case–control and cohort studies of reproductive outcomes in more representative samples of women included measures of drinking, but meta-analyses of this research yield disparate conclusions about alcohol-exposure. Fan et al. (2017) inferred a linear association between decreased fecundability and each additional drink per day. But another review (Van Heertum & Rossi, 2017) concluded that the relation of light/moderate alcohol consumption to female fertility "is yet to be characterized". A third review (de Angelis et al., 2020) found that studies relating alcohol use to women's reproductive fertility "pose more questions than answers".

Prospectively studying a large, population-based sample of Finnish twins, we associated their drinking differences, self-reported at ages 18–25, with lifetime childlessness and eventual number of children in a 33-year follow-up. We distinguished associations of early drinking with childlessness in all twins from associations with eventual family size among twins who had children. These between-family comparisons of twins as individuals were followed by within-twin pair analyses associating drinking patterns with number of children in genetically identical (monozygotic or MZ) twins and same-sex dizygotic (DZ) pairs, who, on average, share half of their genetic variation. Within-twin pair comparisons control between-family confounds with the unique strengths of a co-twin control design.

With data from a large population-based twin sample, our analyses have two major aims:

1. To study long-term predictive associations of patterns of alcohol use at ages 18–25 with lifetime childlessness and to distinguish those from associations with family size among those who eventually did have children.
2. To extend previous research on samples of unrelated singletons with fixed-effects within-twin pair comparisons to control shared familial and genetic confounds.

In secondary analyses reported in Appendix S1, we studied parents' age at birth of their first child and separately analyzed drinking-reproductive associations in individual women and men and within-twin pair analyses of twin sisters and brothers to compare effects of alcohol exposure at ages 18–25 with lifetime reproductive outcomes among women with those of men.

Finland offers an informative context for this study. Despite relatively high overall fertility levels (1.86 for women born in 1950), childlessness is common. Among Finnish men and women aged 40–44, it is the highest among 20 European countries. An analysis of "Childlessness in Finland" (Rotkirch & Miettinen, 2017) notes its high prevalence among both men and women from the least educated groups, suggesting that part of the explanation is that men and women in the least educated groups are also less likely to have found a partner. Of the several reasons for lifetime childlessness (including motivated intent and infertility), the analysis concluded "not having a partner remains the strongest single reason among Finns". Only 4–5% of the entire Finnish population say they never wanted to have children: "Most childless Finns, approaching the end of their reproductive lives are not childless by choice or through infertility" (Rotkirch & Miettinen, 2017).

Another context for our analyses is provided by the single prospective study we found that relates drinking patterns to reproductive outcomes in a large general population sample of women. Eggert et al. (2004) investigated long-term associations of self-reported alcohol consumption with total reproductive outcomes among >7400 Swedish women, ages 18–28, linking the women to hospital records for deliveries (and pregnancy-related hospitalizations) over an 18-year follow-up. Half of the study sample was 18–25, the age of our sample. Alcohol use was assessed by questionnaire before follow-up began: 23% of the women reported abstinence or very infrequent drinking, while 7% met a Swedish health definition of "high" alcohol use. Higher levels of drinking were associated with a lower number of first-born children: with moderate drinkers as the reference, a relative risk (RR) of lower rate of first childbearing (0.73) was observed among women consuming >140 grams alcohol (10–12 drinks) weekly. But both high and low consumption associated with fewer deliveries. The authors offered "a negative influence of alcohol" to explain the association with heavy drinking, and to explain the lower frequency of childbearing among abstainers, they speculated that low consumers "may have had difficulties finding partners" in Sweden during the follow-up period, 1970s to mid-1980s.

MATERIALS AND METHODS

Sample

We analyzed data from a population-based sample of Finnish twins born 1950 through 1957 who completed a baseline questionnaire in 1975, when 18–25 years old (Kaprio et al., 2019). Individual-level

analyses were made of all twins who completed the baseline questionnaire items on alcohol use and who, in January 2009, were linked to Finland's Population Register Centre (PRC) to obtain information on live births recorded for each of them. Linkage was via unique personal identifying codes assigned to all Finns at birth. A total of 8298 individual twins were available for analyses of childlessness and family size. The sample included 500 unpaired twins, 3899 same-sex twin pairs: 1840 twin brothers, 2059 twin sisters. But 236 of these twin pairs (133 brothers, 113 sisters) remain of uncertain zygosity; with their exclusion, 1193 confirmed MZ and 2470 DZ twin pairs remained for within-pair MZ/DZ analyses. Linkage to the PRC revealed that both co-twins in 893 MZ and 1873 DZ pairs had at least one child for studying family size.

Zygosity classification was made from questionnaire items included in the 1975 questionnaire; these items are standard self-assessments of the similarity of appearance in childhood and the frequency of confusion of co-twins' identity by parents, teachers, and others. The validity of zygosity classification from such questionnaire items is well-established (Sarna et al., 1978) and, for many pairs in this sample, has been confirmed with DNA. As expected for Finnish twins in birth cohorts from the early 1950s, two-thirds of same-sex twins in our sample are DZ.

METHODS

Alcohol consumption in 1975; registry linkage on lifetime fertility

The baseline questionnaire assessed frequency (never to over 16 days a month) and quantity (never to 48 bottles of beer/week, >10 bottles of wine/week, or 20 bottles of spirits/month) of alcohol use, both reported separately for beer, wine, and spirits; from these questionnaire reports, we estimated individual consumption in grams/month. Among male twins in this sample, consumption ranged from 0 to 9108 grams per month, with mean consumption of 373 g/month; for female twins, the range was 0 to 3523 g/month with mean of 148 g/month; 12% of the men and 17% of the women reported no use of alcohol at the 1975 baseline. Linkage to Finland's PRC provided information on all children born between 1966 through the end of 2008, covering births to members of our sample across ages 16 to 51.

PRC information on live births was linked to all participants via their unique PINs. In 2009, the twins were 52–59 years old: the reproductive age of women over (no woman in our sample gave birth after 2003), and that of men effectively completed (a single birth among men in our sample occurred in 2009). Paternal uncertainty in this sample is unlikely, because the proportion of Finnish children born without a known biological father is estimated to be <2% (Rotkirch & Miettinen, 2017).

At follow-up in 2009, 75% (6255) of the individual twins in our sample had become parents of one or more biological children, while 1140 men (29%) and 903 women (21%) remained childless. Mean

family size among all fertile twin parents was 2.28 for men and 2.21 for women.

Analytic strategy

We distinguished childlessness from family size, because its association with lifestyle choices and social behaviors, reproductive planning, biological influences, and familial background may differ. We first performed individual level (IL) analyses of associations of alcohol use at ages 18–25 with lifetime number of children among all twins, with corrections made to standard errors to accommodate the non-independence of twins (Williams, 2000). The IL analyses quantify drinking-fertility associations at a population level without adjustment for shared environmental and genetic factors, and they also permit direct comparisons of these associations in men and women from a nation-wide population-based sample. Analyses of twins as individuals were followed by fixed-effects within-pair regression models of all pairs of twin brothers and twin sisters, collapsed on zygosity, and of all MZ and DZ twin pairs, collapsed on sex. To study childlessness, Cox regression survival models were used, estimating the risk of remaining childless by modeling age at first child's birth from the time of questionnaire response until end of follow-up, while censoring for deaths and date of emigration, to yield the correct hazard ratios. We employed Poisson regression, explicitly designed to model count data, to study the number of children, both for twins as individuals and in fixed-effects within-pair models. In secondary analyses, we excluded all childless twins to study age-at-birth of first child with linear regression; results are found in supplemental materials (Tables S5 and S6).

Within-pair analyses were made with fixed-effects regression models, described by Allison (2008). Fixed effects models were developed for (and are widely used in) longitudinal panel data (Gunasekara et al., 2014) in which estimates of exposure-outcome associations are made only on longitudinal variation within individuals. But they apply equally well in analyses of twin data, in which only variation within pairs is modeled, as illustrated, e.g., by Fujiwara and Kawachi (2008, 2009), Aaltonen et al. (2015), and Pettersson et al. (2015). This design accounts for all shared environmental confounds (measured or unmeasured), in all twin pairs and, within MZ pairs, who share all their genes, all genetic confounds, as well (and 50% of genetic confounds in within-pair comparisons of DZ twins). We evaluated predictive associations of baseline drinking with lifetime reproductive histories with a within-pair estimator comparing fertility outcomes among co-twins who differed in baseline drinking at ages 18–25. In stratified within-pair Cox regression models, each twin pair, including pairs with data from only one co-twin, is entered into analysis as a separate stratum. Comparing within-pair results from population-based samples of MZ and DZ twins to the IL results from twins as individuals yields important information on confounds from environmental and genetic sources in all drinking-fertility associations. Our analyses used Stata, version 15 (State Corp, 2015).

Adjustments in analyses

Two adjustments were made in all analyses. The first adjusted for smoking status. Smoking and drinking are highly correlated behaviors, the amount of tobacco smoked correlating with the amount of alcohol consumed (Batal et al., 1995). Smokers are more likely to drink, to drink more frequently, and to consume higher amounts. Associations of drinking with childlessness and number of children are inevitably confounded by the within-individual relationship of drinking and smoking. And smoking elevates risk of infertility, reported in a research review decades ago (Augood et al., 1998). Cumulative research since that review led the American Society for Reproductive Medicine to conclude that effects of smoking on decreased fertility are consistent with a dose–response relationship from an exposure level of one-half pack per day (Practice Committee of the American Society for Reproductive Medicine, 2018).

Smoking was assessed in the 1975 baseline questionnaire with multiple questions (Kaprio & Koskenvuo, 1988). We used four categories to adjust analyses for smoking status: never-smokers, those who reported they had smoked but not more than 100 cigarettes lifetime, "occasional smokers," those who had smoked more, but never on a daily or almost-daily basis, and "regular smokers," distinguished into former and current daily smokers. At baseline, 46% of male twins and 36% of female twins reported they were then daily smokers; an additional 5% of males and 3% of females met criteria as occasional smokers. The prevalence of baseline smoking among twins in our sample did not differ from the general Finnish population at that time.

A second adjustment was made for level of educational attainment. Both childlessness and number of children vary with education in Finland (Nisén et al., 2013; Jalovaara et al., 2019), with higher likelihood of a first birth among better educated, more socio-economically advantaged Finnish men (Nisén et al., 2018). Lifetime childlessness is most common among less educated men and women, and the majority of those who remain childless have either never cohabited or married or have histories of serial short cohabitation (Jalovaara, 2022). And among Finnish women born in the years of our female twins, use of oral contraceptives varied with educational attainment, more commonly used by more educated women (Pasila, 2011). We used the four categories of educational attainment described for this sample of twins in Nisén et al., 2013. Adjustment for both eventual educational attainment and baseline smoking status was made in both individual level and within-pair analyses.

Because some twins had children born before baseline assessment of alcohol use, analyses were made on both the full sample and a restricted subsample. Children born before baseline assessment of the twins' drinking raise issues of reverse causation. Early parenthood may lead to increased (or decreased) drinking, confounding our research intent to study whether early drinking affects later parenthood. To examine this possibility, we report parallel results first excluding, and then including twin parents of children born before baseline from both IL and within-pair analyses; tabular presentations permit side-by-side comparison of results from the full sample with subsamples of twin parents for whom all children were born after baseline assessments were completed.

Use of oral contraceptives was assessed in the baseline questionnaire administered to female twins, with OC use categorized as "never" (reported by 69.2% of the women at ages 18–25), "past use" (14.4%), and "currently using" (16.3%). In individual-level analyses of women, adjustment for baseline OC use was included in models that adjusted also for educational attainment and smoking status of childlessness and number of children.

RESULTS

Our sample of individual twins contained 3981 men and 4317 women. When they completed the baseline questionnaire in 1975, 81% of the men and 70% of the women were single (or divorced); 85% were then consuming alcohol, and at the start of 2009 (the year in which they reached ages 52–59), 75% of all twins in the sample (2841 men, 3414 women) had one or more biological children recorded in Finland's PRC. Linkage revealed that 12% of the children of these parents, including nearly 23% of the firstborn children, had been born in 1975 or earlier, prior to (or at the time of) baseline assessment of their alcohol use.

Descriptive results presented in Table 1 show distributions of alcohol consumption, with the drinks per day measure arrayed from zero to four or more, and its association with fertility outcomes of childlessness (Table 1a) and number of children (1b). Results of individual and within-pair analyses of the data illustrated in these tabular associations follow in Tables 2–5. Childlessness was studied in the full sample of twins; number of children was studied in the subsample of individual twins for whom the population registry linked biological children and to twin pairs in which one, or both twins had at least one child. The number of individuals and twin pairs for each analysis is specified in all tables.

Patterns of alcohol consumption at ages 18–25

At baseline, when aged 18–25, 11% (439/3981) of the men and 17% (735/4317) of the women reported they were consuming no alcohol (Table 1a, upper rows). Among those using alcohol, we converted their reported frequency and quantity of consumption into an estimate of grams consumed per month and using the standard estimate of 12 grams in one drink, created a categorical measure of alcohol exposure by converting grams/month into drinks per day. That derived measure of frequency of drinking is informative for our analysis, and it is the type of frequency measure widely used in previous research linking alcohol exposure to reproductive history. But it is here descriptively misleading, because the most common pattern of drinking among adult Finns in the 1970s limited alcohol use to weekends and holidays, with little or no drinking on other days. Traditional drinking patterns

TABLE 1 Association of Drinking at ages 18–25 with lifetime childlessness and number of children. (a) Lifetime Childlessness among all Men and Women by Drinks per Day in 1975. (b) Mean Number of Children among all non-Childless Men and Women by Drinks per Day in 1975

		Drinks per day in 1975					
(a)		**None**	**1**	**2**	**3**	**4 or more**	**Total**
Men	Total N	439	2278	589	332	293	3981
	Childless N	199	547	172	109	111	1140
	% Childless	40.70	24.10	29.20	32.83	37.64	28.64
Women	Total N	735	3269	212	58	42	4317
	Childless N	238	581	52	18	14	903
	% Childless	32.38	17.82	24.53	26.47	33.33	20.92
		Drinks per day in 1975					
(b)		**None**	**1**	**2**	**3**	**4 or more**	**Total**
Men	Mean	2.76	2.26	2.22	2.10	2.10	2.28
	SD	1.76	0.99	0.97	0.99	0.99	1.11
	N	290	1729	417	223	182	2841
Women	Mean	2.54	2.17	2.06	2.02	1.86	2.21
	SD	1.83	1.00	1.01	1.04	0.89	1.17
	N	497	2679	160	50	28	3414

continued into the 1990s, with high-density drinking on weekends, and neither daily drinking, nor drinking with meals common (Metso & Simpura, 1997).

Table 1a also shows the expected sex differences in alcohol use: 91% of the non-abstinent women, against 64% of non-abstinent men were consuming at the modal level – the equivalent of 1 drink per day. Conversely, over 8% of men, but only 1% of non-abstinent women reported consuming the monthly equivalent of ≥4 drinks per day.

Associations of drinking patterns with childlessness

Childless twins in our sample included 1140 men and 903 women (lower rows of Table 1a). One-fifth (21%) of all women in our sample remained childless on follow-up. Women who were abstainers when 18–25 constituted 17% of their sample, but they accounted for 26% of those who were childless. Among women consuming alcohol at baseline, a dose–response association of drinking with childlessness was apparent: Table 1a illustrates an almost doubling linear increase in childlessness, from 18 to 33%, with increasing levels of consumption. Similarly, abstinent 18-25-year-old men constituted 12% of their sample but accounted for 17% of childless men on follow-up. And as for women, results for non-abstinent men showed a dose–response association of drinking with childlessness, linearly increasing across the four categories of increased consumption. One-third or more of men and women drinking the monthly equivalent of ≥4 drinks per day were childless at follow-up, and for both, heavy drinking at ages 18–25 predicted eventual childlessness as strongly as did abstinence. Table 1 suggests a U-Shaped association of baseline

consumption with lifetime childlessness: the highest levels of childlessness were found among those not drinking at all and, conversely, among those drinking at the highest level of consumption.

Number of children

Among both men and women, increasing consumption of alcohol at age 18–25 was linearly associated with fewer children at follow-up. Table 1b associates the number of children with patterns of alcohol consumption reported in 1975 by all twins not childless at follow-up. For the combined sample, the mean number of children linearly declined across the five categories of drinks per day from 2.62 for those abstaining, to 2.07 for those consuming the equivalent of four or more drinks daily, and the strength of that association is similar for men and women. Men and women who were abstaining when ages 18–25 include those most likely to remain childless, as well as those who eventually will have the most children.

Cox survival models of childlessness

The likelihood of ever having a child was analyzed with Cox regression survival models, first at the individual-level for all twins as individuals, then by stratified fixed-effect models of all MZ and DZ twin pairs to evaluate shared environmental and genetic confounds. Men were more likely childless than women at all levels of drinking, but there was no sex by drinking interaction ($\chi^2 = 2.81$, $p = 0.59$), and we report IL and within-pair results for MZ and DZ twin pairs collapsed on sex. But to permit comparing drinking associations with

TABLE 2 Likelihood of ever having a child associated with drinking at ages 18–25: Cox regression, individual-level analysis

	Twin parents of children all born after 1975 N = 6922			Adding twin parents with one or more children born ≤1975 N = 8298			Full twin sample adjusted for education and smoking[a] N = 8285		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Sex[a]	1.238	[1.16,1.32]	<0.001	1.351	[1.28,1.43]	<0.001	1.429	[1.35,1.52]	<0.001
Drinks per Day in 1975									
None	0.652	[0.59,0.72]	<0.001	0.699	[0.59.0.72]	0.001	0.681	[0.62, 0.74]	<0.001
One	1.000	[1.00,1.00]							
2	0.904	[0.82,1.00]	0.049	0.814	[0.74,0.99]	<0.001	0.814	[0.74, 0.89]	<0.001
3	0.787	[0.69,0.90]	<0.001	0.738	[0.66,0.84]	<0.001	0.756	[0.67, 0.88]	<0.001
4 or more	0.753	[0.64,0.88]	<0.001	0.675	0.59,0.78]	<0.001	0.681	[0.59. 0.79]	<0.001
Educational Attainment									
Primary School only							1.000	[1.00, 1.00]	
More than Primary							1.056	[0.98, 1.14]	0.163
Junior High School							0.920	[0.84, 0.99]	0.048
High School and more							0.749	[0.68, 0.80]	<0.001
Smoking Status in 1975									
Never Smoked							1.000	[1.00, 1.00]	
On Occasion							1.082	[0.94, 1.25]	0.273
Former Smoker							1.478	[1.36, 1.61]	<0.001
Current Smoker							1.200	[1.12, 1.28]	<0.001

[a]Wald $\chi^2 = 461$, $p < 0.001$.

childlessness and number of children in men and women, Tables S1 and S2 include individual and within-pair results separately by sex both for childlessness and for number of children.

The unadjusted associations of baseline drinking with the likelihood of having a child for the subsample of all individual men and women whose children were born after baseline are shown in the first column of results in Table 2. The magnitude of each association is shown as a Hazard Ratio (HR) with its 95% confidence interval. Compared to those drinking the equivalent of 1 drink per day, men and women who were abstaining at baseline were 35% less likely to have a child. Among the majority who were drinking, there is a linear trend of decreasing likelihood of ever having a child with increasing levels of consumption. Compared to the reference group drinking one drink/day, the likelihood of ever having a child is 10% less for men and women drinking two drinks daily, increasing to 21% for those averaging three drinks/day and to 25% at four or more. And at each level of drinking, the difference from the reference group was statistically significant. Comparative results after adding twin parents of children born before baseline assessment of drinking are presented in the middle column of Table 2. The magnitude of all associations is but little altered in the full sample, with narrower confidence intervals for the linear trend of increased likelihood of childlessness with increased levels of consumption. A trend test of linear effects from one to four or more drinks/day estimated the

decrease to average 10% for each additional drink (95% CI from 6% to 14%). To examine and test the proportional hazards assumption of the Cox regression models, we used graphical methods and a global test based on Schoenfeld residuals. We found no evidence that the assumption was violated, with p values of the global test of 0.49 for women and 0.35 for men, and the graphical tests showing parallel curves in the "log–log- curves".

Results for men and women (shown in Table S1) are similar for the association with baseline abstinence and for the linear trend of increasing likelihood of lifetime childlessness with increasing drinking greater than one drink/day. Figures 1 (men) and 2 (women) in Appendix S1 plot survival curves for childlessness and show that effects of drinking habits are stable across lengthy follow-up for both men and women.

Adjusting the Cox survival model for baseline smoking and educational attainment in the full sample yields results shown in the third column of Table 2. Results are effectively unchanged: the linear trend between greater drinking and reduced likelihood of ever having a child remains, with similar magnitude and all associations of both abstinence and levels of drinking with the likelihood of having a child remain significant.

At baseline, nearly a third of all women in the sample were currently using, or had used, oral contraceptives, and baseline OC use was strongly associated with patterns of alcohol consumption. Drinking/

TABLE 3 Likelihood of ever having a child associated with drinking at ages 18–25: Cox regression, within-twin pair analyses. (a) Monozygotic Twin Pairs. (b) Dizygotic Twin Pairs

(a) Monozygotic twin pairs	MZ twin parents of children all born after 1975 N = 902 pairs			Adding MZ twin parents with one or more children born ≤1975 N = 1193 pairs			Full MZ twin sample adjusted for education and smoking[a] N = 1193 pairs		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Drinks per Day in 1975									
None	0.976	[0.73,1.66]	0.635	1.127	[0.75. 1.69]	0.564	1.084	[0.72, 1.67]	0.702
One	1.000	[1.00, 1.00]							
2	0.816	[0.55, 1.22]	0.322	0.815	[0.55, 1.22]	0.316	0.813	[0.54, 1.22]	0.316
3	0.899	[0.55, 1.97]	0.674	0.890	[0.54, 1.46]	0.643	0.889	[0.54, 1.46]	0.642
4 or more	0.378	[0.19, 0.77]	0.007	0.374	[0.18, 0.76]	0.006	0.380	[0.19. 0.77]	0.008
Educational Attainment									
Primary School only							1.000	[1.00, 1.00]	
More than primary							0.953	[0.67, 1.35]	0.788
Junior High School							0.883	[0.56, 1.40]	0.597
High School or More							0.713	[0.38, 1.33]	0.288
Smoking Status in 1975									
Never Smoked							1.000	[1.00, 1.00]	
On Occasion							1.094	[0.61, 1.96]	0.764
Former Smoker							1.250	[0.83, 1.87]	0.278
Current Smoker							1.064	[0.73, 1.54]	0.742

(b) Dizygotic twin pairs	DZ twin parents of children all born after 1975 N = 1845 pairs			Adding DZ twin parents with one or more children born ≤1975 N = 2470 pairs			Full DZ twin sample adjusted for education and smoking[b] N = 2470 pairs		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Drinks per Day in 1975									
None	0.711	[0.54, 0.94]	0.015	0.690	[0.55, 0.87]	0.002	0.737	[0.58, 0.94]	0.012
One	1.000	[1.00, 1.00]							
2	0.794	[0.61, 1.06]	0.088	0.763	[0.61, 0.96]	0.022	0.726	[0.57, 0.92]	0.008
3	0.585	[0.41, 0.83]	0.002	0.528	[0.39, 0.72]	<0.001	0.496	[0.36, 0.68]	<0.001
4 or more	0.971	[0.63, 1.49]	0.892	0.693	[0.48, 1.00]	0.048	0.663	[0.46, 0.96]	0.028
Educational Attainment									
Primary School Only							1.000	[1.00, 1.00]	
More than Primary							0.994	[0.82, 1.20]	0.952
Junior High School							0.998	[0.79, 1.26]	0.986
High School and more							0.863	[0.65, 1.14]	0.295
Smoking Status in 1975									
Never Smoked							1.000	[1.00, 1.00]	
On Occasion							0.884	[0.61, 1.29]	0.520
Former Smoker							1.443	[1.15, 1.81]	0.002
Current Smoker							1.379	[1.14, 1.66]	0.001

[a]Wald $\chi^2 = 11.26$, $p = 0.34$.
[b]Wald $\chi^2 = 47.18$, $p < 0.01$.

TABLE 4 Poisson regression model for number of children, childless twins excluded: Individual-level analysis

Full sample of twins with children N = 6255 individual twins	Twin parents of children all born after 1975 N = 4879			Adding twin parents with one or more children born ≤1975 N = 6255			Full twin sample after adjusted for education and smoking[a] N = 6246		
	β	95% CI	p	β	95% CI	p	β	95% CI	p
Sex#	-0.076	[-0.11, -0.05]	0.001	-0.054	[-0.08,-0.03]	<0.001	-0.060	[-0.09,-0.03]	<0.001
Drinks per Day in 1975									
None	0.152	[0.10, 0.20]	<0.001	0.146	[0.10, 0.19]	<0.001	0.135	[0.09, 0.18]	<0.001
One (Reference category)	0.000	[0.00, 0.00]							
2	-0.013	[-0.06, 0.03]	0.556	-0.032	[-0.07, 0.01]	0.118	-0.023	[-0.06, 0.02]	0.251
3	-0.058	[-0.12,-0.00]	0.066	-0.079	[-0.07,0.01]	0.009	-0.073	[-0.13, -0.01]	0.017
4 or more	-0.080	[-0.16,-0.00]	0.037	-0.088	[-0.16,-0.02]	0.014	-0.081	[-0.15,-0.01]	0.024
Educational Attainment									
Primary School (Reference Category)							0.000	[0.00, 0.00]	
More than Primary School							-0.052	[-0.08, -0.02]	0.02
Junior High School							-0.013	[-0.04, 0.02]	0.47
High School and more							0.003	[-0.03, 0.04]	0.86
Smoking Status in 1975									
Never Smoked (Reference category)							0.000	[0.00, 0.00]	
On Occasion							-0.022	[-0.08,0.04]	0.460
Former Smoker							0.010	[-0.03,0.05]	0.576
Current Smoker							-0.028	[-0.06,0.00]	0.058

[a]Wald $\chi^2 = 357$, $p < 0.001$.

abstaining was highly correlated with use/non-use of OCs. More than 90% of the women reporting abstinence at baseline also reported they had never used OCs; they were, nonetheless, more likely childless at the 33-year follow up. Adding OC use into Cox regression modeling of the abstinence-childless association did not diminish the strength of that association; HRs for the association of drinks/day in 1975 with childlessness were unchanged. Nor did the addition of baseline smoking status and level of educational attainment into the Cox model diminish the magnitude of the association of abstinence with lifetime childlessness. Using women drinking 1 drink per day as the reference group, the likelihood of childlessness among abstaining women in the unadjusted model yielded an HR of 0.641 (95% CI = 0.566–0.725), an HR of 0.668 (0.588–0.756) after adding contraceptive use into the model, and 0.678 (0.594–0.774) after additionally including both smoking status and educational attainment.

Results of the Cox regression survival models for MZ and DZ twins are reported in Table 3 (3a for MZs; 3b for DZs). Within-twin pair results parallel those found for twins as individuals, whether excluding (results in first column) or including (second column) twin parents of children born before baseline. Excluding all parents of children born prior to baseline from within-twin pair analyses of childlessness widened confidence intervals (first column, Tables 3a,b), but the association of the highest level of drinking with a greater likelihood of childlessness remained robust within MZ twin pairs (HR = 0.378, p = 0.007), in a direct test of reverse causation.

For the larger sample of DZ twins, unadjusted within-pair results replicate those found for twins as individuals (Table 3b). HRs are of similar magnitude, and although CIs are somewhat wider, all associations with abstinence and heavier drinking remain significant. Except at the highest level of drinking, associations found in within-pair analyses of MZ co-twins are smaller, and associations within MZ pairs reached significance only at the highest consumption level of >4 drinks/day. Nor was childlessness significantly associated with abstinence among MZ pairs, in direct contrast to the significant associations found in all analyses of individual twins and in within-twin pair analyses of DZ twins. That result suggests genetic confounds may underlie associations of abstinence at 18–25 with lifetime childlessness. The smaller associations of drinking with childlessness in MZ twins, reaching significance only at the highest level of consumption, could reflect a threshold effect in which an association is evident only after high exposure. Adjusting for smoking and education effected little change in hazard ratios for either MZ or DZ twins and significance levels were unchanged (results shown in the third column, Table 3a,b).

Number of children

Individual-level results of Poisson regression of number of children by baseline alcohol consumption are shown in the first column of Table 4 for the subsample of non-childless individual twins whose children were all born after baseline. Abstinence is predictive of a larger number of children at follow-up. Drinking 3 or 4 drinks per day significantly predicts fewer children, with only a modest reduction in effect size of regression coefficients found for the full twin sample (results shown in second column). For the full sample, a significant positive association between baseline abstinence and a larger number of children (0.146 more; 95% CI: 0.10 – 0.19) was found. Among those not abstaining at baseline, drinking more than 1 drink per day progressively predicted fewer children, significantly so at the level of 3 or 4 drinks/day. Regression coefficients were slightly attenuated when adjusted for baseline smoking status, but linearly increased with each level of drinking greater than the reference category of 1 drink per day. Consuming 3 or 4 drinks/day remained significantly predictive of smaller families after adjustment for smoking and education (third column, Table 4).

Adjusting for OC use, as well as smoking and education, in individual-level Poisson models of female twins had negligible effect on magnitude of the associations. The linear trend of increased childlessness with increased consumption found in unadjusted analyses remains after adjustment for OC use, with HRs for number of children of .876, .800, .770 for those consuming 2, 3 and ≥4 drinks/day. Additional adjustments for smoking and educational attainment effected little change. Results of within-pair analyses with fixed-effects Poisson models appear in Table 5: 5a for MZ twin parents; 5b for DZ twins. Results for twins whose children were born after the 1975 baseline are shown in the first column of both tables. HRs for these restricted samples mirror those found for the full samples, shown in the middle column. In contrast to individual-level results, all within-pair associations of abstinence with eventual number of children are negative relative to the reference of one drink a day, with an effect size greater than −0.20 in MZ and greater than −0.11 among DZ twin parents. The negative association of heavier drinking with family size found in analyses of individual twins was confirmed in within-pair analyses of DZ twin pairs at each level of consumption beyond the reference category of one drink a day. Within MZ twins, an association was evident only at the highest level. But the effect size of that association was substantial: an estimated 0.45 fewer children than that observed for the reference group. That result parallels the association of levels of drinking with childlessness in MZ twins; both results are consistent with threshold effects, reaching significance only at elevated level of consumption. Adjustment for baseline smoking status and education (third columns, Table 5) had negligible effect on within-pair associations relating drinking patterns to family size. The use of OCs did not diminish the association of either abstinence or heavy drinking (>4 drinks/day) with fewer children, nor were these associations reduced after adding smoking status and educational attainment to within-pair Poisson models.

DISCUSSION

This prospective 33-year follow-up associated drinking patterns during late adolescence/early adulthood with the likelihood of lifetime

TABLE 5 Poisson regression for number of children: Within-twin pair analyses. (a) Monozygotic Twin Pairs. (b) Dizygotic Twin Pairs

(a) Monozygotic Twin Pairs	MZ twin parents of children all born after 1975 N = 736 pairs			Adding MZ twin parents with one or more children born ≤1975 N = 1027 pairs			Full MZ twin sample adjusted for education and smoking[a] N = 1023 pairs		
	β	95% CI	p	β	95% CI	P	β	95% CI	p
Drinks per Day in 1975									
None	−0.282	[−0.56,-0.00]	0.048	−0.202	[−0.41, 0.00]	0.051	−0.196	[−0.40,0.01]	0.064
One	0.000	[0.00, 0.00]							
2	0.031	[−0.22, −0.29]	0.811	0.017	[−0.19, 0.23]	0.872	0.007	[−0.20, 0.22]	0.948
3	0.009	[−0.30, −0.32]	0.042	−0.012	[−0.27, 0.24]	0.923	−0.003	[−0.26,0.25]	0.983
4 or more	0.452	[−0.89, −0.01]	0.954	−0.482	[−0.84,-0.12]	0.008	−0.492	[−0.86,-0.13]	0.008
Educational Attainment									
Primary School only							0.000	[0.00, 0.00]	
More than Primary							−0.104	[−0.28, 0.07]	0.245
Junior High School							0.074	[−0.16, 0.30]	0.526
High School and more							0.063	[−0.24, 0.37]	0.686
Smoking Status in 1975									
Never Smoked							0.000	[0.00,0.00]	
On Occasion							0.087	[−0.22,0.39]	0.571
Former Smoker							−0.027	[−0.23,0.17]	0.790
Current Smoker							−0.047	[−0.24,0.14]	0.624

(b) Dizygotic twin pairs N = 2249 DZ pairs	DZ twin parents of children all born after 1975 N = 1624 pairs			Adding DZ twin parents with one or more children born ≤1975 N = 2249 pairs			Full DZ twin sample adjusted for education and smoking[b] N = 2244 pairs		
	β	95% CI	p	β	95% CI	P	β	95% CI	p
Drinks per Day in 1975									
None	−0.136	[−0.28, 0.01]	0.062	−0.110	[−0.23, 0.01]	0.071	−0.103	[−0.22, 0.02]	0.094
One	0.000	[0.00, 0.00]							
2	0.120	[−0.26, 0.02]	0.098	−0.172	[−0.29,-0.05]	0.005	0.120	[−0.26, 0.02]	0.098
3	0.218	[−0.40, −0.04]	0.018	−0.224	[−0.38,-0.07]	0.004	−0.167	[−0.29,-0.04]	0.007
4 or more	- 0.233	[−0.47, −0.01]	0.055	−0.233	[−0.43,-0.04]	0.018	−0.229	[−0.42,-0.03]	0.021
Educational Attainment									
Primary School only							0.000	[0.00, 0.00]	
More than Primary							0.076	[−0.02, 0.17]	0.129
Junior High School							0.046	[−0.07, 0.16]	0.444
High School and more							0.085	[−0.05, 0.22]	0.234
Smoking Status in 1975									
Never Smoked							0.000	[000. 000]	
On Occasion							−0.047	[−0.24, 0.14]	0.624
Former Smoker							0.183	[0.07, 0.30]	0.002
Current Smoker							0.003	[−0.09, 0.10]	0.952

[a]Wald $\chi^2 = 15.46$. $p = 0.116$.
[b]Wald $\chi^2 = 35.075$, $p < 0.001$.

childlessness distinguishing those from associations with eventual family size. To evaluate confounds, we compared individual-level analyses of a population-based sample of twins to within-pair fixed-effects analyses of twin pairs nested within the same sample. All analyses were adjusted for baseline smoking and educational attainment; individual-level analyses of female twins were additionally adjusted for OC use. And our analyses offer direct comparisons of associations of alcohol-exposure with reproductive histories of men and women drawn from the same population-based birth cohorts.

What insights have these novel analytic comparisons yielded? Four sets of results are noteworthy: strong predictive associations of baseline abstinence with both childlessness and number of children; linear associations among non-abstainers between increasing levels of their drinking and eventual number of their children; the modest effects of adjustment for smoking, EA and OC use, and the finding that associations observed for men parallel those found among women, both as individuals and within twin brothers and sisters. The U-shaped predictive association of baseline abstinence with our outcomes is noteworthy. Lifetime childlessness was very common among men and women who reported no alcohol use at baseline; 40% of abstaining men and nearly one-third of abstaining women were childless on follow-up 33 years later. Conversely, abstinent men and women who later did have children, tended to have more. Among the large majority in our sample (89% of men, 83% of women) who reported alcohol use at ages 18–25, more frequent drinking was linearly predictive of lifetime childlessness. And that association held among both men and women (results found in Table S1). Among men reporting baseline drinking equivalent to four or more drinks daily, childlessness was nearly as common as for men reporting abstinence. And within the small sample of women drinking that heavily, childlessness was just as prevalent as among women who reported no use of alcohol. The greater likelihood that women abstinent at baseline would be childless at follow-up was not diluted by adding education, smoking and OC use into analyses.

To interpret those associations, it is important to clarify the nature of both our predictor and the outcomes we studied. We have not assessed the motivation or capability to produce offspring. Nor have we assessed individual differences in potential for reproduction. Our sample was created from a population-based sample of all living, resident twins from eight consecutive Finnish birth cohorts, first studied when ages 18–25. Selection was not based on information on reproductive planning or reproductive fitness, for which we have no information. Our sample, born in the 1950s, reached early adulthood at a time when marriage and fertility rates were declining in Finland. And this was the time when control of reproduction first became a matter of personal choice; oral contraceptives became widely available in the late 1960s. At the same time, cohabitation outside of marriage was becoming increasingly accepted (Pasila, 2011). And both abstinence and childlessness are embedded within familial, cohort, and cultural expectations, modulated by personal experiences and religious influences. Abstaining from alcohol use and remaining childless may be personal decisions that have common causal threads. Important in interpreting the abstinence-childless link is another result: abstinent twins at baseline who do reproduce have the largest number of children at follow-up.

It is important, as well, to clarify that baseline drinking patterns not only predict eventual number of children. They also predict continuing drinking patterns over time. Substantial individual and within-pair stability of alcohol use was reported by our studied twins across decades of their follow-up from baseline in 1975 to the fourth assessment during 2011/12 (Virtanen et al., 2019 and unpublished data). The robust predictive associations of baseline drinking with fertility outcomes found in our analyses reflect drinking differences, between and within twin pairs, that endure over decades.

On average, heavier-drinking men and women in our sample had significantly fewer children than normative drinkers with whom they were compared. A major reason for that finding is because heavier drinkers more often remained childless. But deleting those who remained childless and associating drinking patterns with family size among fertile twins confirmed that heavier baseline drinking predicts number of children. Individual-level analyses of all 6255 fertile men and women showed a linear decline in family size across the four categories of increasing alcohol consumption, significantly so at the two highest levels of drinking. And that finding held in separate IL analysis of all men. IL analyses of female twins replicate the association of fewer children with greater drinking, with an even greater regression weight at the highest level of consumption. But few women were drinking at that highest level at baseline; accordingly, confidence intervals are wide, and the association failed to reach significance ($p = 0.08$). But among both men and women, heavier drinking in late adolescence and/or early adulthood negatively predicts family size, with the same trends and with similar effect size among men and women.

Fixed effects within-twin pair models of DZ twins replicated associations found in IL analyses relating level of baseline drinking to eventual size of family. On follow-up, heavier drinking co-twins had significantly fewer children in all pairwise comparisons, including both sisters and brothers, collapsed on zygosity, and, importantly, both MZ and DZ twins, collapsed on sex. Effects were slightly larger among brothers than sisters and among MZ compared to DZ twin pairs. Consistently, lighter-drinking twin individuals, on average, had more children than their heavier-drinking twin siblings. Analyses of drinking discordant MZ twins reveal that these associations are not fully attributable to familial or genetic confounds.

Analyses within twin pairs reversed the positive association of abstinence with family size found in IL analyses. IL associations may be confounded by familial factors and religious attitudes that motivate abstinence and influence family planning, Within-twin pair analyses account for these influences and could result in a negative association. While the mechanism is uncertain, the reversed result obtained from within-family comparisons suggests that shared familial confounds contribute to the association of baseline abstinence with larger number of children.

We explored associations of drinking with age at birth of first child in all individual twins who had children and in within-twin pair comparisons of all pairs in which both co-twins had at least one child. Results of those analyses are in Tables S5 and S6. Abstinence predicted delayed reproduction in all IL analyses. Men who were abstinent at baseline fathered their first child about a year later than men who reported drinking at ages 18–25; results were similar, albeit a bit smaller, for abstinent women. But associations of abstinence with reproductive timing were not found in within-pair analyses, not among twin brothers or sisters, nor within MZ or DZ twin pairs. Nor did our analyses yield consistent associations of age at birth of first child with increased levels of drinking. A sex difference in reproductive timing was evident: abstinent women and those consuming 1 drink per day had their first child about 2 years earlier than men with

the same patterns of abstinence or moderate drinking. But in contrast to the associations of abstinence/drinking to both childlessness and number of children, no consistent patterns were evident in either men or women associating patterns of alcohol use with reproductive timing.

UNCERTAINTIES, LIMITATIONS, AND STRENGTHS

Generalizability of our results to non-twins and to later birth cohorts and other cultures is uncertain. Our sample was composed of twin siblings who experienced an age-matched dyadic relationship unique to twins. Twins do not differ from singletons on multiple dimensions of lifestyle and on major domains of personality (Johnson et al., 2002). Nor do reproductive patterns of female twins differ from those of matched singletons (Christensen et al., 1998). Factors contributing to childlessness in Finland are much like those identified among older childless Americans (Abma & Martinez, 2006; Frejka, 2017; Valerio et al., 2021). But whether our results will generalize across cohorts and cultures is less certain. The predictive associations revealed in our analyses could be conditioned by cohort-specific experiences, because our subjects experienced their reproductive years during a period of sexual and demographic transition and newly available contraception.

Plausible pathways underlying some associations we report remain to be identified. Perhaps abstinence in late adolescence and early adulthood served to place men and women in these birth cohorts at a disadvantage in finding partners. No information on motivations for reproduction or attitudes toward reproductive control were obtained from our twin subjects, and questions of mechanisms by which abstinence and early adult alcohol-exposure predictively associate with men and women's reproductive histories await full answers in future research. Can the abstinence-childlessness association be explained by the notion (advanced by Eggert et al., 2004), that abstinent young adults in Nordic cultures have difficulties finding partners? Could heavy drinking in late adolescence/early adulthood similarly increase likelihood of a partnerless, childless, future? Finally, while completely ruling out confounding genetic effects and effects of environmental factors shared by co-twins, the within-pair analysis of MZ twins is limited by possible confounding effects of unmeasured non-shared environmental factors specific to each person. Thus, within-pair associations do not necessarily reflect causal effects of the exposure.

Acknowledging these uncertainties and limitations, our long-term follow-up study has many strengths. Within-family comparisons of drinking-discordant twins offer convincing evidence that associations of alcohol-exposure with reproductive success cannot be entirely attributed to between-family confounds and factors related to one's rearing family and shared genetic predispositions. Our inclusion of a parallel sample of twin brothers demonstrated that associations of alcohol exposure with childlessness and total fertility are as evident in men as among women and are of similar magnitude. Our samples were population-based,

prospectively studied, and results offer a heuristic set of findings for future research to pursue.

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