The Impact of Unemployment on Antidepressant Purchasing

Adjusting for Unobserved Time-constant Confounding in the g-Formula

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Background: The estimated effect of unemployment on depression may be biased by time-varying, intermediate, and time-constant confounding. One of the few methods that can account for these sources of bias is the parametric g-formula, but until now this method has required that all relevant confounders be measured.

Methods: We combine the g-formula with methods to adjust for unmeasured time-constant confounding. We use this method to estimate how antidepressant purchasing is affected by a hypothetical intervention that provides employment to the unemployed. The analyses are based on an 11% random sample of the Finnish population who were 30–35 years of age in 1995 (n = 49,753) and followed until 2012. We compare estimates that adjust for measured baseline confounders and time-varying socioeconomic covariates (confounders and mediators) with estimates that also include individual-level fixed-effect intercepts.

Results: In the empirical data, around 10% of person-years are unemployed. Setting these person-years to employed, the g-formula without individual intercepts found a 5% (95% confidence interval [CI] = 2.5%, 7.4%) reduction in antidepressant purchasing at the population level. However, when also adjusting for individual intercepts, we find no association (−0.1%; 95% CI = −1.8%, 1.5%).

Conclusions: The results indicate that the relationship between unemployment and antidepressants is confounded by residual time-constant confounding (selection). However, restrictions on the effective sample when using individual intercepts can compromise the validity of the results. Overall our approach highlights the potential importance of adjusting for unobserved time-constant confounding in epidemiologic studies and demonstrates one way that this can be done.

Keywords: Confounding; Depression; g-formula; Selection; Unemployment

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Depression is a leading cause of disability in both men and women, and a major public health concern globally.[1–3] The worldwide prevalence of depression has increased in recent decades and is expected to continue increasing.[4] One determinant of depression is unemployment.[5,6] Unemployment can result in loss of financial means, social contacts, and purposeful activity, all of which increase the risk of depression.[5–7] From the reverse perspective, depression is a risk factor for unemployment, as individuals suffering from depression may experience greater difficulty in finding and retaining employment.[8,9]

Because of the interrelationships between unemployment and depression, many methods will struggle to estimate an unbiased causal effect of unemployment on depression.[8,10] Given their time-dependent relationship, a longitudinal design is imperative. Furthermore, various determinants, such

as physical health or partnership status, may affect both un-employment and depression, i.e., they may function as (time-varying) confounders. At the same time, such determinants may also be affected by unemployment or depression them-selves. Confounders that are affected by prior exposures are also known as intermediate confounders.[11,12] Most traditional statistical techniques cannot account for time-varying and intermediate confounding.[13]

The g-formula is one of the few methods that can be used to model complex longitudinal dependencies, including time-varying and intermediate confounding.[14–16] The g-for-mula has been used before to model the complex interrelation-ships between unemployment and antidepressant purchasing, an indicator of diagnosis of depression.[5] An earlier study found that, among young adults entering the labor market for the first time, reducing unemployment is estimated to result in less antidepressant purchasing, especially for low-educated men.[5] However, unobserved time-constant confounding may affect the estimates in that study.

A typical way to adjust for unobserved or person-level time-constant confounding (henceforth "unobserved time-constant confounding") when using longitudinal data is to in-clude individual-level fixed-effect intercepts.[17] By including such intercepts, only exposures that change over time con-tribute to an estimated effect. As such, the influence of time-constant determinants, including unmeasured time-constant confounders, is eliminated. Although this method is relatively common across the quantitative social sciences, we are not aware of any previous research that combines the method with the parametric g-formula, despite the potential advantages of such an approach.

The aims of this study are therefore two-fold. First, we aim to determine the population-level effect of eliminating unemployment on antidepressant purchases among a cohort of men and women in Finland who were 30–52 years old from 1995 to 2012. Second, we aim to demonstrate a new approach to causal inference that combines the parametric g-formula to account for time-varying confounders that are affected by prior exposures, with individual-level fixed-effect intercepts to account for unobserved time-constant confounding.

METHODS

Study Population

We study a closed cohort of Finnish men and women in calendar years 1995–2012. All individuals are 30–35 years of age at the start of follow-up, and 47–52 years at the end. The sample size is 49,753 individuals, with right-censoring of 2,693 individuals. The study includes 826,526 person-years, with intermediate censoring of 4,743 person-years.

Data Source

The data source for this study is an 11% random sample of the population permanently residing in Finland at the end of 1995 that is updated each calendar year. Statistics Finland constructed these data by linking individual-level census records, death records, and labor market records to social care records, sickness absence allowance records, and medication records maintained by the Social Insurance Institution of Fin-land (permission code TK-53-339-13).

Outcome Variable

Our outcome is antidepressant purchasing, an indicator variable measuring whether an individual has purchased an antidepressant (ATC N06A) or an antidepressant in combi-nation with psycholeptics (ATC N06CA) in a calendar year.

Time-varying Exposures, Mediators, and Confounders

All time-varying variables are measured annually and function simultaneously as exposures, mediators, and poten-tial confounders. The primary exposure of interest is employ-ment status, categorized as employed, unemployed, retired, or other (including students). In addition, we have time-varying information on household status, income, and other drug pur-chases. Household status is categorized as "child living with parents," "single without children," "single with children," "cohabiting without children," "cohabiting with children," "married without children," and "married with children." Income is measured using personal income after taxation and household disposable income including nontaxable in-come. Both income types are continuous variables measured in euros and corrected for inflation (reference year = 2014). Household disposable income was also divided by the number of consumption units present in the household using the Organisation for Economic Co-operation and Development (OECD)-modified scale (OECD, 2013). Other drug purchases are measured using 11 binomial variables recording the pur-chase of: antibacterials (ATC J01), opioids (N02A), antipy-retic and analgesics other than opioids (N02B), psycholeptics (N05), psycholeptics other than antidepressants (N06, but not N06A or N06CA), sex hormones (G03), drugs for obstruc-tive airway diseases (R03), antihistamines (R06), beta block-ers (C07), renin–angiotensin agents (C09), and antiprotozoals (P01). We also adjust for age in 5-year categories (30–34, 35–39, 40–44, 45–49, and 50–52).

Time-constant Variables

Time-constant variables are sex (female or not), lan-guage spoken at home (Finnish, Swedish, or other), and high-est educational level (lower secondary, higher secondary, lower tertiary, or higher tertiary—International Standard Classification of Education (ISCED) 2011 categories 2, 3–4, 5–6, 7–8, respectively).

Effect Estimation

We estimate the effect on antidepressant purchasing of setting all unemployed person-years to employed throughout follow-up. We assume a set of 1-year cross-lagged rela-tionships between the time-varying variables, allowing for
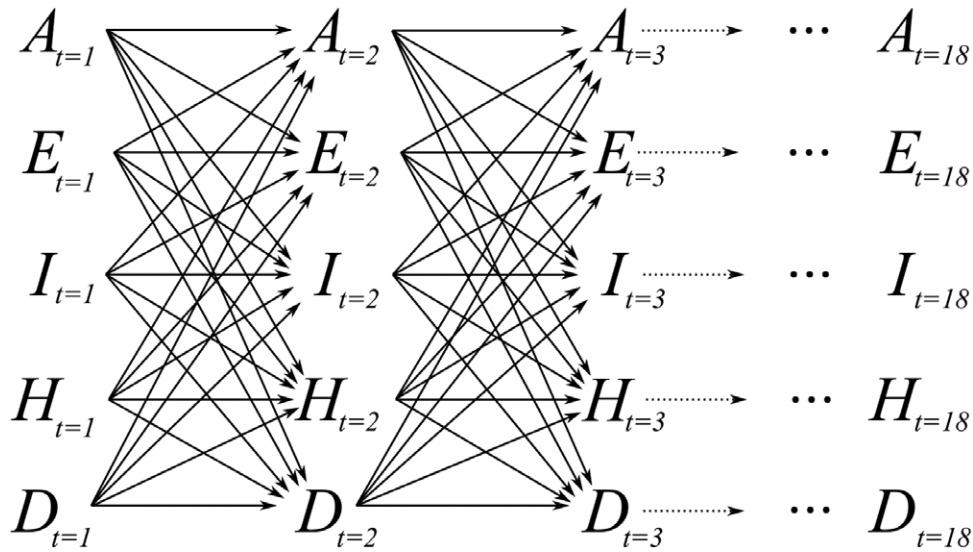
FIGURE 1. Assumed causal directed acyclic graph (DAG) showing antidepressant purchasing (A), employment status (E), income (I), household status (H), and purchases of drugs other than antidepressants (D). Time-constant variables (not shown) were allowed to affect all time-varying variables.

mediation (Figure 1). Time-constant variables, when included in the analysis, are allowed to affect all time-varying variables at every time point. To estimate the effect of our hypothetical intervention, we apply the parametric g-formula using a series of steps that we describe in eAppendix 1 (http://links.lww.com/EDE/B474) and have also been described extensively elsewhere (e.g., Refs [5], [14], and [18]). Two steps of this approach are of special interest: an estimation step and a prediction step. In the estimation step, we estimate three sets of multivariable linear probability models. Linear models allow for the inclusion (and extraction) of individual fixed intercepts in a computationally efficient manner, compared with a g-formula with individual intercepts and nonlinear (i.e., generalized linear) models. The first two sets are estimated using models specified as follows:

$$V_{i,t}^h = \eta^h + \boldsymbol{B}_i^\top \boldsymbol{\beta}^h + \boldsymbol{V}_{i,t-1}^\top \boldsymbol{\mu}^h + \boldsymbol{L}_{i,t-1}^\top \boldsymbol{\lambda}^h + e_{i,t}^h \qquad (1)$$

where $\boldsymbol{V}$ is a vector containing all time-varying variables, with h to denote a specific time-varying variable (the models are estimated for every V^h except age), i as an index for individuals in the sample, and t for time in calendar years (Table 1). $\boldsymbol{B}$ contains the baseline variables, $\boldsymbol{L}$ represents interaction terms between employment status and sex, and between employment status and education, and we assume $e_t^h \sim N(0, \sigma_h^2)$. Equation 1 is estimated using covariate sets 1 (time-constant covariates") and 2 (time-constant and time-varying covariates) from Table 1. To analyze the role of time-constant confounding, we then estimate a third set of models which replace the intercept η^h and the baseline variables $\boldsymbol{B}$ with individual-level fixed-effect intercepts, labeled θ_i^h, which we call covariate set 3 (Table 1). These models are specified as:

TABLE 1. Covariates Included in the Three Different Covariate Sets

Covariate Groups	Notation	Variable Names	Set 1	Set 2	Set 3
Time constant	$\boldsymbol{B}$	Sex	X	X	
		Language	X	X	
		Education	X	X	
Time varying	$\boldsymbol{V}$	Antidepressant purchasing		X	X
		Employment status	X	X	X
		Household status		X	X
		Income		X	X
		(Other) drug purchases		X	X
		Age		X	X
	$\boldsymbol{L}$	Employment status × sex	X	X	X
		Employment status × education	X	X	X
Individual intercepts	θ	Individual intercepts			X

$$V_{i,t}^h = \theta_i^h + \boldsymbol{V}_{i,t-1}^\top \boldsymbol{\mu}^{h\prime} + \boldsymbol{L}_{i,t-1}^\top \boldsymbol{\lambda}^{h\prime} + e_{i,t}^{h\prime} \qquad (2)$$

Using the steps of the g-formula as described in the eAppendix 1; http://links.lww.com/EDE/B474, these models are then used to predict antidepressant purchasing (V^{AD}) for a scenario in which no hypothetical intervention is performed on employment (V^{Emp} kept at empirically observed values v^{Emp}) termed $E[V^{AD}(v^{Emp})]$ and is also known as the "natural course scenario," and to predict antidepressant purchasing in a

scenario in which V^{Emp} is changed so that no individual is unemployed ($\bar{v}^{\text{Emp}}$), denoted as $E[V^{\text{AD}}(\bar{v}^{\text{Emp}})]$ and termed the "hypothetical intervention scenario." These expectations represent the total number of person-years with at least one antidepressant purchase, divided by all person-years in the study. The effect of the hypothetical intervention is then estimated as $E[V^{\text{AD}}(\bar{v}^{\text{Emp}}) - V^{\text{AD}}(v^{\text{Emp}})]$.

Each time-varying variable is predicted in sequence annually from $t = 1995$ to $t = 2012$ using covariate values from the year before. When using covariate sets 1 and 2, predictions are made for individuals by inserting covariate values into Eq. 1 and adding a random draw from $N(0, \sigma_h^2)$. For binary and multinomial outcomes, predicted probabilities are then used to draw values (0 or 1) from binomial and multinomial distributions, respectively.

When using covariate set 3, predictions are made by inserting covariate values into Eq. 2, adding a random draw from $N(0, \sigma_h^{2'})$, and drawing from binomial or multinomial distributions where applicable. However, it is important to note that when estimating with covariate set 3, the intercepts θ_i^h are estimated for all individuals, but only those individuals who vary on the time-varying variables V contribute to the estimation of the corresponding μ' and λ' coefficients. Hence, when predicting using covariate set 3, the individuals in the sample ($i = 1 \dots n$) can be broken down into two groups: those who vary on any of the time-varying variables V, referred to here as group Q, and those who do not vary on any of the time-varying variables V, group O, with $Q \cup O = N$. The sizes of both groups are termed n_Q and n_O, respectively, and $n_Q + n_O = n$. If we use the empirical data to make predictions from our estimated models (i.e., the natural course scenario), then the average of a variable V_h in the population at time t can be estimated as:

$$\hat{E}(V_t^h) = \frac{1}{n}\sum_{i \in N}(\hat{\theta}_i^h) + \frac{1}{n_Q}\sum_{i \in Q}(V_{i,t-1}^\top \hat{\mu}^{h'} + L_{i,t-1}^\top \hat{\lambda}^{h'}) \quad (3)$$

where hats represent that parameters are estimates from Eq. 2. In Eq. 3, the first term can be seen as containing the between-individual variation for the whole sample, and the second term as containing the within-individual variation for those who vary on any of V.

Both between-individual and within-individual differences contribute to the population-averaged estimate of the level of an outcome V^h in a scenario, such as $E[V^{\text{AD}}(\bar{v}^{\text{Emp}})]$. However, when including individual intercepts in the multivariable estimation, only within-individual differences contribute to the hypothetical intervention effect estimate $E[V^{\text{AD}}(\bar{v}^{\text{Emp}}) - V^{\text{AD}}(v^{\text{Emp}})]$, because $\hat{\theta}_i$'s of both scenarios will cancel out. Furthermore, empirically, many individuals only change on a few time-varying covariates V and thereby contribute to only a few of the estimated coefficients μ' and λ' in any of the multivariable models. The models with individual-level fixed-effect intercepts therefore have different effective sample sizes for each coefficient (Table 2). In addition,

TABLE 2. Transitions in Key Variables

Variable	Individuals (%)	Person-years (%)
Antidepressant purchase	28.7	4.4
Employment status	50.9	10.8
Household status	65.4	7.8
Income	99.6	99.3

Percentage of individuals (total = 49,753) with at least one transition, and number of person-years (total = 826,526) representing a transition. An income transition refers to any change in income.

effects can only occur for those individuals whose covariates change as a consequence of the hypothetical intervention, i.e., those for whom $V(v^{\text{Emp}}) \neq V(\bar{v}^{\text{Emp}})$. However, not all who belong to the $V(v^{\text{Emp}}) \neq V(\bar{v}^{\text{Emp}})$ group experience a change on each covariate V^h empirically and therefore do not contribute to the corresponding $\mu^{h'}$ and $\lambda^{h'}$ coefficients, but our approach transports the estimated μ' and λ' coefficients to all individuals who have $V(v^{\text{Emp}}) \neq V(\bar{v}^{\text{Emp}})$.

The models with individual-level fixed-effect intercepts (Eq. 3) were estimated using the "plm" package in R.[19] Annotated R code performing the g-formula for sets 2 and 3 is available in eAppendices 2 and 3; http://links.lww.com/EDE/B475 and http://links.lww.com/EDE/B476, respectively.

Subgroup and Sensitivity Analyses

We perform additional analyses to gain further insight into our results. First, we estimate effects by education (secondary and tertiary levels) and sex, because previous research has shown that effects can differ between these groups.[5]

Second, introducing individual-level intercepts into the modeling procedure reduces the sample that contributes to effect estimation. To gain some insight into the degree to which the change in sample changes our results, we additionally perform the g-formula with covariate set 2 on the population of individuals who changes their employment status, i.e., all individuals who remain constantly employed or unemployed throughout follow-up are removed from this sample.

Third, the estimation of all three covariate sets is also performed with hospitalization because of injuries and accidents (International Classification of Diseases, 10th Revision codes: S00-T79, T90-T98) instead of antidepressant purchasing. Compared with antidepressant purchases, this outcome is less likely to be sensitive to differences in treatment-seeking behavior between social strata.

A sensitivity analysis investigating the strength of potential (unobserved) time-constant confounding can be found in the eAppendix 1; http://links.lww.com/EDE/B474.

RESULTS

Descriptive Findings

Of the study cohort, 18% have lower secondary as their highest education, 48% higher secondary, 24% lower tertiary,

and 9% higher tertiary. The registered language of 94% of the cohort is Finnish, 4% Swedish, and 2% other. The percentage of men is 50%.

Antidepressants are purchased by 3% of cohort members in 1995, increasing over time (as individuals age) to 11% in 2012, with 8% on average. In 1995, 16% of all individuals are registered as unemployed, decreasing to 6% at the end of follow-up, with 10% on average. Around 11% of unemployment spells last 5 consecutive years or more. From 1995 to 2012, the percentage employed increases from 71% to 84%, with the discrepancy between the decline in unemployment and the rise in employment caused by changes in other categories (retired or other). In 1995, the average yearly taxable income is €22,090, rising to €35,600 in 2012.

g-Formula Results: No Unemployment Versus Natural Course

Our hypothetical intervention sets all unemployed person-years (10.2% of all person-years) to employed. We use three covariate sets to estimate the effect of this scenario on antidepressant purchases (Table 1). The g-formula's natural course scenario from the richest measured covariate set (set 2) appears to approximate the empirical data adequately (see eAppendix 1; http://links.lww.com/EDE/B474). Covariate sets that do not include individual-level fixed-effect intercepts (sets 1 and 2) all estimate some population-level reduction in annual person-years with antidepressant purchases (Figure 2). For the set with the most measured covariates (set 2), both time constant (sex, language, and education) and time varying (income, household status, other drug purchases, and previous antidepressant purchases), the hypothetical intervention reduces antidepressant purchasing by 5%. Comparing
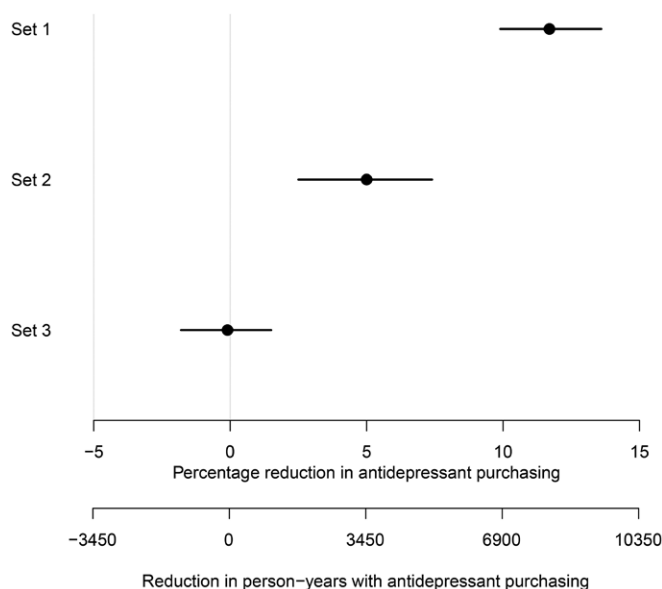
covariate sets 1 and 2 shows that including time-varying variables attenuates effect estimates.

Covariate set 3 adjusts for unobserved time-constant confounders by including individual intercepts. This covariate set did not find an effect, suggesting that reducing unemployment among those who have experienced unemployment may not reduce antidepressant purchases.

Models additionally including 2- and 3-year lags for all covariates and outcomes were also fitted but did not substantially alter our conclusions. The results of all multivariable models used in our g-formula procedures can be found in eAppendix 4; http://links.lww.com/EDE/B477.

Subgroup and Sensitivity Analyses

The differences found between the covariate sets largely persist in each stratum of our subgroup analysis (Table 3). In the sets without individual intercepts (1 and 2), effect estimates of the hypothetical intervention are stronger for the low educated compared with the high educated and are closer to a null association for women than for men. Reflecting the overall analysis, null associations are found for all subgroups when including individual intercepts (set 3).

Roughly half (25,355) of all individuals in the sample experienced at least one change in their employment status during follow-up. Performing the g-formula with covariate set 2 on this population showed a population-averaged reduction in antidepressant purchasing of 3.8% (95% confidence interval [CI] = 0.6%, 7.0%).

Finally, we find that the effect of our hypothetical (no unemployment) intervention is similar for hospitalization because of injury or accident, as compared with antidepressant purchasing. The effect is slightly stronger than for antidepressant purchasing, but the analysis including individual-level fixed-effect intercepts (set 3) also found no effect despite high precision (Figure 3).

DISCUSSION

The estimated effect of unemployment on antidepressant purchasing may be biased by time-varying, intermediate,

FIGURE 2. Forest plot of the population-averaged effect of making all unemployed person-years employed on antidepressant purchasing (negative values indicate an increase).

TABLE 3. Effect of Making All Unemployed Person-years Employed on Person-years of Antidepressant Purchasing (Negative Values Indicate an Increase) by Subgroup

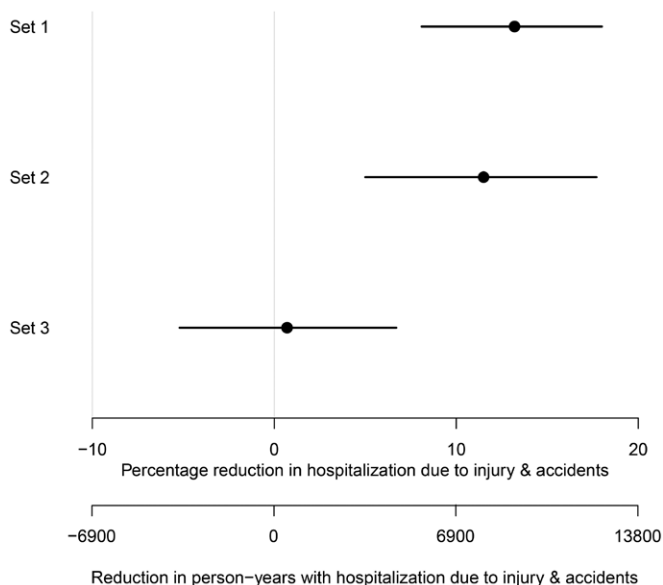| Covariate Set	Low Educated % Reduction (95% CI)	High Educated % Reduction (95% CI)
Men		
Set 1	21.6 (18.1%, 24.9%)	10.5 (4.1% to 16.8%)
Set 2	9.5 (4.7%, 13.9%)	2.8 (−5.5% to 11.0%)
Set 3	1.0 (−2.3%, 4.0%)	0.3 (−5.5% to 5.8%)
Women		
Set 1	9.8 (6.8%, 12.7%)	4.3 (0.4%, 8.1%)
Set 2	4.2 (0.5%, 7.9%)	0.8 (−4.5%, 5.8%)
Set 3	−0.9 (−3.5%, 1.5%)	−0.5 (−3.9%, 2.9%)

FIGURE 3. The population-averaged effect of making all unemployed person-years employed on hospitalization because of injury or accident (negative values indicate an increase).

and time-constant confounding. The parametric g-formula is one of the few methods that can account for these sources of bias but has previously required that all relevant confounders be measured. For the first time (to our knowledge), we combine the g-formula with methods to adjust for unobserved time-constant confounding. We estimate the effect of a hypothetical intervention which sets all unemployed person-years (10.2% of all person-years) to employed on antidepressant purchasing. The covariate sets that do not include individual-level fixed-effect intercepts estimate a reduction in the number of person-years with antidepressant purchasing when compared with the natural course. The reduction is estimated to be 5% points (95% CI = 2.5%, 7.4%), population-averaged, in the covariate set that includes time-varying covariates and which most closely follows our assumed directed acyclic graph. However, when including individual-level fixed-effect intercepts to remove unobserved time-constant confounding, the estimate becomes −0.1% points (95% CI = −1.8%, 1.5%).

Strengths and Limitations

Our data constitute an 11% random sample of register data, extracted and anonymized by Statistics Finland following data protection regulations. To limit the influence of potential cohort effects, we choose to follow a closed cohort with a small age range (30–35 years followed until 47–52 years). Furthermore, the age range was chosen because the vast majority of participants have finished education by the age of 30, and because of the increased probability of leaving the labor market for reasons other than unemployment at ages of 50 and above.

Since missingness on covariates is very small (<1%) we do not use missing data imputation methods. The exception is employment status, which has 4.6% missingness. Using a multiple imputation procedure for this variable, including all time-constant and time-varying covariates, does not substantially alter the findings of this study. Furthermore, our natural course scenario of covariate set 2 closely approximates empirical antidepressant purchases, and all other time-varying covariates, which indicates that our models are not grossly misspecified.[5,16]

Antidepressant purchases do not perfectly indicate the presence of depression. In Finland, only about a third of those with major depression or anxiety disorder received antidepressant treatment.[20] However, the specificity of antidepressant purchases is about 90%, and the majority of individuals purchasing psychotropic medication are likely to have a mental health condition.[20–23] Furthermore, prior research shows that psychotropic drug purchases are associated with depression and suicide, and react to adverse life events such as divorce and workplace downsizing.[20–28] In addition, psychotropic medication purchases require a prescription and are thus based on clinical assessments.

Individuals who become employed may obtain better access to occupational health services, which may increase the probability of a depression diagnosis. It is also possible that higher socioeconomic status individuals and individuals with partners are more likely to receive care.[5] If this were the case, the results of the hypothetical intervention of this study (Figure 2) may be negatively biased. However, it is contested whether unmet need for treatment is higher among individuals in low socioeconomic positions, and Finnish population-based studies indicate that income is unrelated to whether or not an individual with a mental health disorder receives treatment.[20,29–33]

The causal claims of this study rely on three fundamental assumptions: consistency, positivity, and no unobserved confounding.[34–36] The consistency assumption requires that there are no different versions of the exposure that have different effects on the outcome. Strictly speaking, different types of employment may have different effects on mental health, which affects the external validity (generalizability) of our study. We reflect on this in later paragraphs. The positivity assumption requires that observed treatment levels vary within confounder strata. In our empirical data, employment status varies within the strata of all measured covariates. Importantly, our study adjusts for unobserved time-constant confounding using individual-level fixed-effect intercepts and observed time-varying confounding. To the best of our knowledge, we are the first to do so using the parametric g-formula. It is possible that by restricting our analysis (through the use of individual intercepts) to the group that has experienced changes in employment status, the influence of time-varying confounders becomes more prominent. Thereby, adding individual-level intercepts may compromise internal validity, potentially biasing effect estimates even if we restrict our inference to the population of changers.[37] We include a large set

of potentially important time-varying confounders; however, it remains possible that some time-varying confounding is unobserved. For example, unobserved health shocks may influence both employment status and antidepressant purchasing. Although we are not able to adjust for this, we believe this form of bias in our study is small, since the hypothetical intervention effect is also small.

Unobserved Time-constant Confounding

When including the individual intercepts into the modeling procedure, the hypothetical intervention effect becomes null. As indicated by our subgroup analysis, the null effect is also found across educational and sex strata. This could indicate the presence of strong time-constant factors that affect both unemployment and antidepressant purchasing. The sensitivity analysis that performs the g-formula without individual intercepts on the subsample of those who change their employment status showed only a 1.2% point lower reduction in antidepressant purchasing compared with the ordinary set 2 estimate. This may indicate that only a small part of the change in the estimate between the g-formulas with and without individual intercepts is due to the effect being estimated for a qualitatively different population. However, this is not certain; due to having multiple time-varying covariates, most individuals who do not vary on employment still vary on other variables, and thereby contribute to the coefficients of those variables. These contributions are now also lost from this sensitivity analysis' estimate.

In the sensitivity analysis where we replace antidepressant purchasing with injuries and accidents as the outcome variable, conclusions reflect those of the main analysis. Not adjusting for individual intercepts results in a hypothetical intervention effect that reduces injuries and accidents, but adjusting for individual-level intercepts results in a null estimate. This finding is important because unemployment and hospitalization due to injuries and accidents are likely to be partly affected by time-constant factors similar to those that also affect unemployment and depression (or antidepressant purchasing), such as early problem behavior, childhood adversity, and personality traits such as neuroticism and lack of conscientiousness.[38–40] At the same time hospitalization due to injuries and accidents as an outcome is less sensitive to selection through care-seeking behavior, compared with antidepressant purchasing. Therefore, these findings imply that differences in care-seeking do not explain our results.

The Unemployment Effect

The association between employment status and antidepressant purchasing may be explained by time-constant factors that make individuals both more prone to be unemployed and to purchase antidepressants, though it may also be explained by a change in meaning and generalizability of the employment effect in the model with individual-level intercepts. Time-constant factors may include poor childhood physical and mental health, adverse childhood socioeconomic conditions

or personality traits such as neuroticism and lack of conscientiousness.[38–40] The findings of our study corroborate those of other studies that found no effects of unemployment on mental health when including individual intercepts to adjust for unobserved time-constant confounding.[41,42] A third study using individual intercepts found only weak estimated effects of unemployment on health, and large selection into unemployment and poor health.[43] However, it is important to note that adding individual intercepts to the modeling procedure also changes the meaning of the coefficients in the multivariable models, and thereby the results of a g-formula procedure that uses these coefficients. When including individual-level fixed-effect intercepts, the only observations that contribute to the estimation of relevant coefficients are those where the exposure varies over time.[17] In our study, on average 10.2% of person-years were unemployed, and roughly half of all individuals were continuously employed throughout the study. Individuals in the ages of 30–55 years who spent a year unemployed are likely to be qualitatively different from individuals who have not spent any time unemployed (as measured annually). The type of employment that they can obtain may also differ qualitatively. Individuals who switch regularly between unemployment and employment are more likely to experience precarious employment. Various studies have found that those in precarious employment, such as temporary employment or employment with weak social protections, and those transferring to such jobs have higher mental health risks than those in nonprecarious employment.[44–47] This is not to imply that the estimates of the covariate set with individual intercepts should be disregarded. Some employment interventions may result in less fulfilling and more precarious forms of employment and may therefore be better approximated by the g-formula with individual intercepts.

CONCLUSIONS

To our knowledge, this is the first study–of any exposure or outcome–to combine individual-level fixed-effect estimation with the parametric g-formula in order to adjust for unobserved time-constant confounding. We use this method to study the impact of unemployment on antidepressant purchasing. At the population level, without fixed-effect intercepts, we find a substantial reduction in antidepressant purchasing in a scenario where everyone is employed. However, when we include individual-level fixed-effect intercepts, we estimate a null effect. We argue that this null effect arises not only due to the adjustment for unobserved time-constant confounding but also due to a change in the meaning and generalizability of the effect of employment in models with individual-level fixed-effect intercepts.

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