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Comparison of modeling strategies to study the effect of an exposure on changes in continuous outcomes: evaluating the impact of alcohol consumption on changes in cardiometabolic health markers based on the German National Cohort (NAKO)

Martina Bouka[1,2], Katharina Nimptsch[1,3], Ulrike Grittner[4], Solange Gonzalez Chiappe[1], Gertraud Maskarinec[1,5], Annette Peters[6,7,8,9], Claudia Meinke-Franze[10], Hansjörg Baurecht[11], Heiko Becher[12], Henry Völzke[10], Hermann Brenner[13], Isti Rodiah[14], Lilian Krist[15], Michael Leitzmann[16], Nadia Obi[17], Peggy Sekula[18], Stefan N. Willich[15], Rafael Mikolajczyk[19], Tobias Pischon[1,20,21,*]

[1]Molecular Epidemiology Research Group, Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany
[2]Institute for Public Health, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
[3]Epidemiology Research Group, Faculty of Health Sciences Brandenburg, University of Potsdam, Potsdam, Germany
[4]Department for Biostatistics and Clinical Epidemiology, Centre for Stroke Research, Charité - Universitätsmedizin Berlin, Berlin, Germany
[5]Population Sciences in the Pacific, University of Hawai'i Cancer Center, Honolulu, HI, United States
[6]Institute of Epidemiology, Helmholtz Zentrum München—German Research Center for Environmental Health (GmbH), Neuherberg, Germany
[7]Chair of Epidemiology, Institute for Medical Information Processing, Biometry and Epidemiology, Medical Faculty, Ludwig-Maximilians-Universität München, Munich, Germany
[8]DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany
[9]German Center for Diabetes Research (DZD e. V.), Neuherberg, Germany
[10]Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany
[11]Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany
[12]Heidelberg Institute of Global Health, University Hospital Heidelberg, Heidelbreg, Germany
[13]Cancer Prevention Graduate School, German Cancer Research Center (DKFZ), Heidelberg, Germany
[14]Department of Epidemiology, Helmholtz Zentrum für Infektionsforschung, Brausnchweig, Germany
[15]Institute of Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, Germany
[16]Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany
[17]Institute for Occupational and Maritime Medicine (ZfAM), University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[18]Institute of Epidemiology and Prevention, Faculty of Medicine and Medical Center—University of Freiburg, Freiburg, Germany
[19]Institute for Medical Epidemiology, Biometrics, and Informatics, Interdisciplinary Center for Health Sciences, Medical Faculty of the Martin Luther University Halle-Wittenberg, Halle, Germany
[20]Biobank Technology Platform, Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany
[21]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
*Corresponding author: Max-Delbrück-Centrum für Molekulare Medizin (MDC), Robert-Rössle-Straße 10, Building 42-53, Room 2125, 13125 Berlin, Deutschland. E-mail: tobias.pischon@mdc-berlin.de

Abstract

Background **When investigating effects of baseline exposures on changes in continuous outcomes in longitudinal studies, the change-score model is increasingly recommended, while baseline adjustment is debated. Limited empirical evidence exists on the extent to which these choices matter. We examined how different modeling strategies influence estimated effects using alcohol and prospective changes in cardiometabolic health markers as an example.**

Methods **We used data from the German National Cohort (NAKO; ∼205 000 participants at baseline, ∼140 000 at 4–5-year follow-up). Participants reported alcohol consumption at baseline (2014–19) and were classified as light, moderate, heavy, former, or never drinkers. Triglycerides (TG), systolic and diastolic blood pressure (SBP and DBP), high-density lipoprotein cholesterol (HDL-C), and glycated hemoglobin were measured at baseline and 5 years later. Longitudinal effects were**

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estimated using a change-score model informed by directed acyclic graphs without baseline adjustment, and compared to a baseline-adjusted model and a model that adjusted for the average of baseline and follow-up (Oldham's). Statistical tests assessed whether changes in the outcome depended on baseline levels.

Results **Change-score and Oldham's models produced highly consistent results across all five cardiometabolic markers, whereas baseline-adjusted change-score models yielded different results for all. Statistical tests assessing the relationship between baseline levels and subsequent change did not indicate whether baseline adjustment would materially alter the results. Based on the change-score models, former drinkers had lower 5-year TG change and higher SBP, DBP, and HDL-C changes compared with light drinkers, while heavy drinkers had lower DBP change.**

Conclusion **When exposure precedes the baseline outcome, baseline adjustment in change-score analyses may substantially alter effect estimates.**

Keywords longitudinal, modeling, cardiometabolic markers, alcohol

Key Messages

- We examined how different common longitudinal modeling strategies affect estimates of exposure on changes in continuous outcomes, using alcohol consumption and 5-year changes in cardiometabolic markers as an applied example.
- Change-score and Oldham's analyses produced highly consistent results across all five cardiometabolic markers, whereas the change-score adjusted for baseline produced substantially different results, even with small effects, and statistical tests assessing whether the amount of change depends on the baseline value did not necessarily indicate whether adjusting for baseline would change the substantive findings.
- Based on the consistent findings across change-score and Oldham's models, former drinkers had lower 5-year TG change and higher SBP, DBP, and HDL-C changes compared with light drinkers, while heavy drinkers had lower DBP change.

Introduction

Besides epidemiological investigations of hard disease endpoints, modeling prospective changes in health-related biomarkers is increasingly used in preventive research to better understand health-to-disease transition. Longitudinal analysis can answer the question of how prior exposures relate to outcome changes over time.

A common approach to answer this question is the change-score model, in which within-person change is calculated as the difference between follow-up and baseline values and analyzed as the outcome [1]. Some researchers suggest adjusting the change-score for the baseline values to account for initial individual differences [2]. However, this practice is being questioned [3]. Debates in recent research highlight that baseline-adjusted change-score models may be prone to biases including regression to the mean (RTM) and mathematical coupling, especially when baseline measurement errors are present [1, 3–9]. Although correction methods have been proposed [10], they often rely on strong assumptions and are applied as a sensitivity analysis.

To address these concerns, Tu and Gilthorpe [9] revisited, among others, Oldham's method [11], which assesses whether change depends on baseline by examining the association between change and the average of baseline and follow-up values. This idea was extended into a regression framework adjusting change for this average. When exposure precedes the baseline outcome value (e.g. when past alcohol consumption is reported at baseline and blood pressure (the outcome) is measured at the baseline visit), Dukes *et al.* [12], guided by directed acyclic graphs (DAGs) suggested the change-score model as a valid approach. Glymour [4] further demonstrated that if baseline values affect follow-up values only through physiological continuity (i.e. measurements of the same underlying construct at different time points), baseline-adjusted and unadjusted change-score models estimate the same effect. However, if baseline values influence developmental processes that affect follow-up, the two models target different estimands. Using simulations, they showed that in the presence of random measurement error, baseline-adjusted models yield biased estimates, whereas unadjusted change-score models remain unbiased.

As an applied example, the aim of this study is to compare the different methodological approaches, using data from the German National Cohort (NAKO) to investigate whether alcohol consumption measured at baseline is associated with 5-year changes in key cardiometabolic indicators. Cardiometabolic biomarkers reflect different aspects of cardiovascular and metabolic function [13–16] and alcohol consumption is a lifestyle behavior shown to influence multiple aspects of cardiometabolic health [17–20], although its impact on longitudinal change remains unclear. Using the unadjusted change-score model as our primary approach, we assess whether, how, and under which circumstances the effect of the exposure differs when alternative methods (change-score model adjusted for baseline and Oldham's method) are applied. For a complementary perspective, we compare longitudinal results with cross-sectional associations to examine whether short-term changes align with patterns observed under more prolonged exposure. Although this study focuses on cardiometabolic indicators, the findings

have broader relevance for studying time-varying health outcomes in observational research.

Materials and methods

Data source

NAKO is an ongoing population-based prospective study designed to investigate the causes and risk factors of common diseases and enhance early detection and prevention [21]. Initiated in 2014, it enrolled ∼205 000 adults by 2019 across 18 study centers in Germany. A follow-up examination conducted 4–5 years later (2018–24) included ∼140 000 participants. Both examinations included standardized interviews, self-administered questionnaires, comprehensive physical and medical examinations, clinical biomarker assessments, and biosample collection [21, 22].

Outcome measures

Cardiometabolic outcomes were selected to represent key components of the metabolic syndrome available at both baseline and follow-up, including lipid metabolism, blood pressure, and glycemic regulation. Outcomes are based on physical measurements or laboratory analyses of blood samples conducted according to a standardized protocol [23] (for measurement details [22, 24], refer to Supplementary Methods): triglycerides (TG, mmol/l), high-density lipoprotein cholesterol (HDL-C, mmol/l), systolic and diastolic blood pressure (SBP, DBP, mmHg) and glycated hemoglobin (HbA1c, mmol/mol), each assessed at both baseline and 5-year follow-up.

Within-person change was calculated as the difference between follow-up and baseline values, standardized to a 5-year interval. This assumes approximately linear change over time, allowing regression coefficients to be interpreted as expected 5-year differences.

Exposure and covariates

Alcohol consumption at baseline was the exemplary exposure of interest. In NAKO, alcohol consumption was assessed using a standardized, self-administered touchscreen questionnaire ascertaining beverage-specific frequency and quantity questions. We categorized current drinkers as light (>0–<5 g/day, reference), moderate (≥5–<15 g/day), or heavy (≥15 g/day) [25]. Additional items on lifetime alcohol use also allowed classification of participants as former or never drinkers.

Covariates were selected a priori as potential confounders (Fig. 1) and included sex, age (in our analysis: centered at 50 years and scaled per 10-year increase), education, and smoking status. Educational attainment was classified using ISCED 97 (International Standard Classification of Education-1997 [26]) levels: “Low” (levels 1–2), “Medium” (levels 3–4), “High (reference)” (levels 5–6), and “In vocational training.” Smoking status was categorized as “Never (reference),” “Former,” or “Current” smoker. Body mass index (BMI) was also considered as an additional covariate and calculated in kg/m^2 using measured weight and height at the baseline exam.

We additionally considered physical activity and diet. Physical activity was assessed as total MET-minutes per week and categorized as low (<500 MET-min/week; <8.3 MET-hours/week), moderate (500–5000 MET-min/week; 8.3–83.3 MET-hours/week), or high (>5000 MET-min/week; >83.3 MET-hours/week) [27, 28]. Diet was assessed using the Modified Mediterranean Diet Score (mMDS), with a theoretical range from 0 to 9 points, among participants with complete dietary data [29].

Statistical analysis

Descriptive statistics were used to summarize participant characteristics at baseline and follow-up. Categorical variables are presented as counts and percentages, while continuous variables are reported as means with standard deviations (SDs).

Cross-sectional analysis

To examine the cross-sectional association between alcohol consumption and the baseline value of each cardiometabolic marker, we used multivariable adjusted linear regression models with robust standard errors [30].

Longitudinal analysis

According to current methodological guidance for longitudinal observational studies [4, 12], our primary analytical approach to estimate the effect of alcohol consumption on changes in cardiometabolic indicators was the change-score model without adjustment for the baseline value of the outcome. Baseline covariates used for adjustment were selected based on DAGs (Fig. 1) and included sex, age, education, and smoking status.

To compare results across modeling strategies, we additionally fitted two alternative models: a change-score model with adjustment for baseline outcome values and Oldham’s model, which adjusts for the average of baseline and follow-up values rather than baseline. In line with Tu and Gilthorpe [9], we also examined whether changes in outcome values were statistically related to their baseline levels, using two diagnostics. First, we calculated the Pearson correlation between the change-score and the average of the baseline and follow-up values, as proposed by Oldham [11]. A substantial correlation—with a value that is not close to zero—suggests that the observed change may systematically be associated with baseline levels. Second, we applied the variance ratio test, which compares the variances of baseline and follow-up measurements while accounting for their correlation. This test yields a t statistic with $n-2$ degrees of freedom; larger departures of this statistic from zero indicate greater differences between baseline and follow-up variances, consistent with possible dependence of observed change on baseline values [9]. These diagnostics were used descriptively and correlations were evaluated by their magnitude rather than significance.

Additional models

We conducted two additional analyses. First, we repeated the linear regression models using the follow-up value of each indicator as the outcome. Second, we fitted linear mixed-effects models with a random intercept for participants to obtain an estimate averaged across baseline and follow-up. Both models included alcohol consumption as the exposure and were adjusted

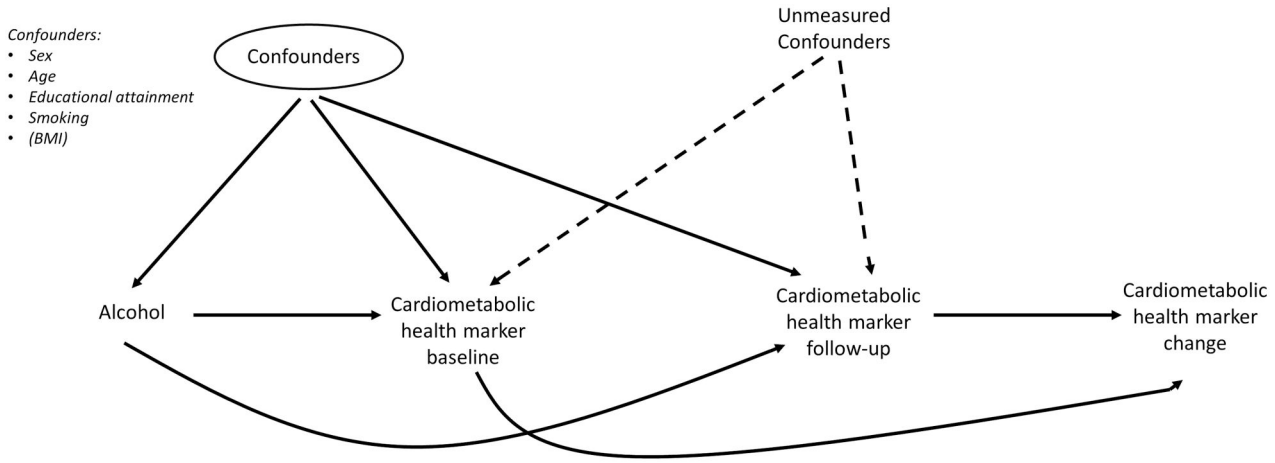


Figure 1 Directed acyclic graph for the estimation of the relationship between alcohol consumption and cardiometabolic health markers' change in the German National Cohort (NAKO) 2014–19. Cardiometabolic health markers include triglycerides (TG), high density lipoprotein cholesterol (HDL-C), hemoglobin A1c (HbA1c), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

for sex, age (centered at 50 years expressed per 10-year increase in age), educational attainment, and smoking status (all at baseline). The mixed-effects model additionally included time as a fixed effect.

The analytical sample was restricted to participants with available data on alcohol consumption at baseline and outcome measurements at both baseline and follow-up. Participants with pre-existing cardiometabolic diseases or using relevant medications were not excluded. Missingness in the main covariates was low (<1%); therefore, analyses were conducted using complete cases (Fig. 2 and Supplementary Table S1).

As part of sensitivity analyses, firstly, we re-estimated all models after including baseline BMI as an additional covariate. Secondly, to examine whether lifestyle factors influenced our main findings, we further adjusted the primary cross-sectional and change-score models for physical activity and the mMDS.

All analyses were implemented in the statistical software R (version 4.5.1).

Results

Participant characteristics

Characteristics of the 204 562 participants are shown in Table 1. Most participants reported current alcohol consumption, with nearly half being light drinkers. Mean cardiometabolic marker levels at baseline and follow-up were generally within expected population ranges. Over the 5-year period, mean values of TG, HDL-C, HbA1c, and SBP increased slightly, while DBP decreased marginally.

Cross-sectional analysis

Compared with light drinkers (reference group), moderate drinkers had lower baseline TG levels, whereas never drinkers had higher TG levels (Table 2, Supplementary Table A). Moderate and heavy drinkers had higher SBP, DBP, and HDL-C levels and lower HbA1c levels, while former and never drinkers showed the opposite pattern.

Longitudinal analysis

The change-score and Oldham's models produced highly consistent estimates across all five cardiometabolic markers, whereas the change-score adjusted for baseline showed differences, with associations appearing, disappearing, or changing direction (Table 3, Supplementary Table B).

For TG, former drinkers had a lower 5-year change compared with light drinkers in both the change-score and Oldham's models [change-score: −0.09 mmol/l, 95% confidence interval (CI): −0.14 to −0.05). The baseline-adjusted model additionally indicated a smaller change among moderate drinkers.

For SBP, the change-score and Oldham's models indicated a higher 5-year change among former drinkers compared with light drinkers (change-score: 0.73 mmHg, 95% CI: 0.25–1.20), with a weak positive association among never drinkers. In contrast, these associations were not observed in the change-score adjusted for baseline, which instead indicated a higher change among heavy drinkers.

For DBP, heavy drinkers had a lower and former drinkers a higher 5-year change compared with light drinkers, and a weak positive association was observed among never drinkers across the change-score and Oldham's models. Baseline adjustment substantially altered these results: the association for heavy drinkers changed direction from −0.15 mmHg (95% CI: −0.30 to −0.01) to 0.30 mmHg (95% CI: 0.18–0.43), a positive association also appeared for moderate drinkers, and the associations for former and never drinkers were no longer observed.

For HDL-C, the change-score and Oldham's models indicated a small higher 5-year change among former drinkers compared with light drinkers. This association was not observed in the baseline-adjusted model, which instead indicated small but higher changes among moderate and heavy drinkers.

For HbA1c, neither the change-score nor Oldham's model indicated associations with alcohol consumption. In contrast, the

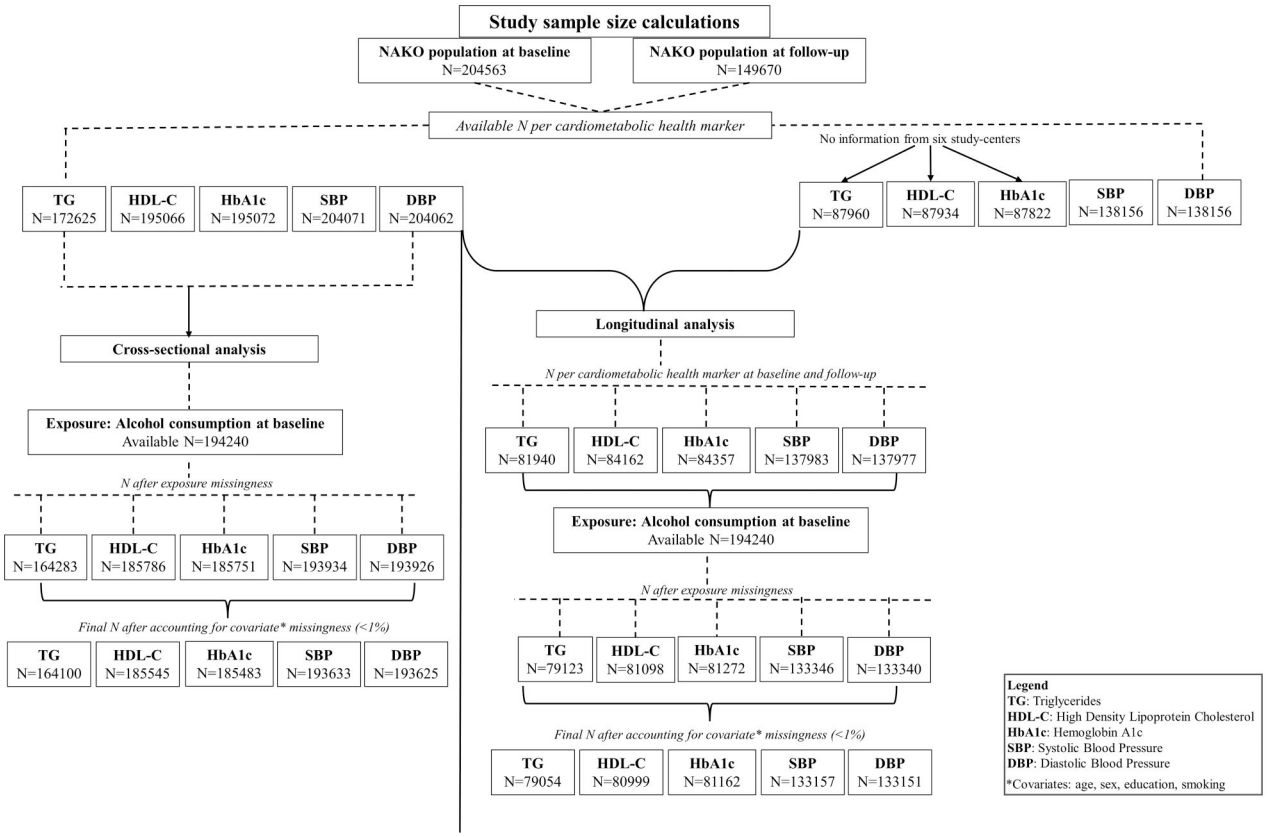


Figure 2 Derivation of the analytical samples for the cross-sectional and longitudinal analyses. Sample sizes are presented separately for each cardiometabolic marker according to data availability for the outcome, baseline alcohol consumption, and covariates. For the longitudinal analyses, participants were required to have measurements of the respective cardiometabolic marker at both baseline and follow-up. Final analytical samples were restricted to participants with complete information on age, sex, educational attainment, and smoking status; covariate missingness was <1%.

baseline-adjusted model indicated lower 5-year changes among moderate and heavy drinkers and higher changes among former and never drinkers compared with light drinkers.

Oldham's test correlations were small for all markers (ranging from −0.060 for TG to 0.10 for HbA1c). Baseline adjustment altered the findings for all five markers, and larger Oldham's test correlations (in absolute number) did not correspond to greater differences between the change-score and the baseline-adjusted model. A similar pattern was observed for the variance ratio test (Table 3).

Additional models

Analyses using follow-up values of each cardiometabolic indicator as outcomes yielded patterns broadly consistent with the cross-sectional findings. Mixed-effects models similarly supported these patterns. Full estimates from the additional models are presented in the Supplementary Material.

Additional adjustment for BMI had little to no impact on estimates across all models. Further adjustment for lifestyle factors (physical activity and diet) in the primary cross-sectional and change-score models also left estimates largely unchanged. Full sensitivity analyses are presented in Supplementary Tables C and D.

Discussion

In this study, we compared three statistical approaches (change-score, change-score adjusted for baseline, and Oldham's) to examine the longitudinal relation between alcohol consumption and cardiometabolic markers as an example. Change-score and Oldham's models produced highly consistent results across all five markers, whereas the change-score adjusted for baseline showed substantially different findings. Associations appeared, disappeared, and, in some cases, changed direction in the baseline-adjusted model, despite the mostly small effects. Moreover, the magnitude of Oldham's test correlations and variance-ratio statistics did not correspond to the extent to which baseline adjustment altered the findings. Based on the change-score models, former drinkers had lower 5-year TG change and higher SBP, DBP, and HDL-C changes compared with light drinkers, while heavy drinkers had lower DBP change. Overall, longitudinal associations were smaller than those observed cross-sectionally.

The discrepancies between the longitudinal models may be explained by several mechanisms. First, when the exposure precedes the baseline outcome, as considered in our case given that alcohol consumption reflects drinking behavior prior to the baseline examination, baseline-outcome adjustment involves conditioning on a post-exposure variable and may introduce collider-

Table 1 Baseline and follow-up characteristics of the NAKO population included in the analysis overall and by sex, 2014–19.

Categorical variables[a]	Overall *N* = 204 562	Female *N* = 103 204	Male *N* = 101 358
Educational attainment			
ISCED 97 low	6552 (3.2%)	3986 (3.9%)	2566 (2.5%)
ISCED 97 medium	84 167 (41.2%)	46 518 (45.2%)	37 649 (37.2%)
ISCED 97 high	109 165 (53.5%)	50 340 (48.9%)	58 825 (58.1%)
Vocational training	4335 (2.1%)	2176 (2.1%)	2159 (2.1%)
Alcohol consumption[b]			
Light drinkers	84 958 (43.7%)	52 937 (54.2%)	32 021 (33.2%)
Moderate drinkers	49 820 (25.6%)	22 425 (23.0%)	2 7395 (28.4%)
Heavy drinkers	42 676 (22.0%)	12 940 (13.3%)	29 736 (30.8%)
Former	8305 (4.3%)	3918 (4.0%)	4387 (4.5%)
Never	8481 (4.4%)	5435 (5.6%)	3046 (3.2%)
Smoking			
Current smoker	43 672 (22.1%)	20 053 (20.3%)	23 619 (24.0%)
Past smoker	63 957 (32.3%)	29 564 (29.7%)	34 393 (35.0%)
Nonsmoker	90 164 (45.6%)	49 811 (50.1%)	40 353 (41.0%)
Physical activity			
High	78 699 (41.7%)	39 256 (41.0%)	39 443 (42.3%)
Moderate	84 582 (44.8%)	43 302 (45.2%)	41 280 (44.3%)
Low	25 648 (13.6%)	13 217 (13.8%)	12 431 (13.3%)

	Continuous variables[c]	Overall, Mean (SD) *N* = 204 562	Female, Mean (SD) *N* = 103 204	Male, Mean (SD) *N* = 101 358	Clinical cut-off[d] (adults)
	Age at baseline	50.0 (12.6)	49.8 (12.6)	50.2 (12.6)	
	BMI at baseline (kg/m^2)	26.7 (5.09)	26.1 (5.6)	27.3 (4.5)	
	Missing	1004	528	476	
	Mediterranean diet adherence score	4.50 (1.81)	4.32 (1.84)	4.69 (1.76)	
	Missing	52 358	25 013	273 45	
TG (mmol/l)	Baseline [*N* = 172 625]	1.7 (1.18)	1.1 (0.9)	2.0 (1.4)	<1.7 mmol/l
	Follow-up [*N* = 87 960]	1.7 (1.1)	1.5 (0.9)	1.9 (1.3)	
HDL-C (mmol/l)	Baseline [*N* = 195 066]	1.5 (0.4)	1.7 (0.4)	1.4 (0.4)	≥1.3 mmol/l (F) ≥1.2 mmol/l (M)
	Follow-up [87 934]	1.6 (0.4)	1.8 (0.4)	1.4 (0.4)	
HbA1c (mmol/mol)	Baseline [195 072]	36.4 (6.6)	36.0 (5.8)	36.8 (7.3)	<39 mmol/mol
	Follow-up [87 822]	37.7 (6.2)	37.4 (5.5)	38.1 (6.9)	
SBP (mmHg)	Baseline [204 071]	128.1 (16.6)	124.1 (16.9)	132.2 (15.3)	<130 mmHg
	Follow-up [138 156]	128.1 (16.4)	124.6 (16.9)	131.6 (15.1)	
DBP (mmHg)	Baseline [204 062]	79.0 (10.0)	77.3 (9.8)	80.7 (9.9)	<80 mmHg
	Follow-up [138 156]	78.2 (9.7)	76.6 (9.6)	79.8 (9.7)	

[a] Categorical values are presented as counts with percentages in parentheses.
[b] Alcohol consumption was categorized as light (>0–<5 g/day), moderate (≥5–<15 g/day), heavy (≥15 g/day), former, and never drinkers.
[c] Continuous values are presented as means with SDs in parentheses.
[d] Clinical cut-offs sourced from Mayo Clinic guidelines (www.mayoclinic.org).

stratification bias, particularly in the presence of unmeasured common causes of the baseline and follow-up outcomes [12]. Baseline adjustment may also introduce biases such as RTM and mathematical coupling. Oldham's method was proposed to address these problems, and its close agreement with the change-score model supports the consistency of the estimates, although it does not establish their absence of bias, as both approaches may share sources of bias. Second, measurement error in the baseline outcome may introduce additional bias when it is included as a covariate, whereas the unadjusted change-score model is relatively protected from this source of bias [4].

Glymour [4] further argues that, when the exposure precedes the baseline outcome, the effects estimated by the change-score and the change-score adjusted for baseline may differ when the baseline outcome influences the follow-up not only through physiological continuity but also through other mechanisms, such as by altering a disease or developmental process. This may also be relevant for the cardiometabolic markers examined in our study. For example, individuals with high HbA1c levels at baseline may subsequently change their diet, lose weight, receive treatment, or make other health-related changes that influence HbA1c at follow-up. In this case, baseline HbA1c

Table 2 Cross-sectional associations between alcohol consumption at baseline and cardiometabolic health markers.

Method Variable	Baseline outcome linear regression Estimate (95% CI)[a]
TG (mmol/L)	
Light drinkers[b]	Ref
Moderate drinkers	−0.05 (−0.06 to −0.04)
Heavy drinkers	−0.01 (−0.03 to 0.00)
Former drinkers	0.00 (−0.03 to 0.03)
Never drinkers	0.09 (0.06 to 0.11)
N[c]	164 100
SBP (mmHg)	
Light drinkers	Ref
Moderate drinkers	0.48 (0.32 to 0.65)
Heavy drinkers	1.75 (1.57 to 1.94)
Former drinkers	−1.76 (−2.12 to −1.41)
Never drinkers	−0.96 (−1.30 to −0.61)
N	193 633
DBP (mmHg)	
Light drinkers	Ref
Moderate drinkers	0.26 (0.16 to 0.37)
Heavy drinkers	1.16 (1.04 to 1.28)
Former drinkers	−1.38 (−1.60 to −1.16)
Never drinkers	−0.60 (−0.82 to −0.39)
N	193 635
HDL-C (mmol/L)	
Light drinkers	Ref
Moderate drinkers	0.10 (0.09 to 0.10)
Heavy drinkers	0.17 (0.17 to 0.18)
Former drinkers	−0.03 (−0.03 to −0.02)
Never drinkers	−0.09 (−0.10 to −0.08)
N	185 545
HbA1c (mmol/mol)	
Light drinkers	Ref
Moderate drinkers	−0.80 (−0.87 to −0.74)
Heavy drinkers	−1.20 (−1.27 to −1.12)
Former drinkers	0.91 (0.74 to 1.09)
Never drinkers	1.17 (1.00 to 1.34)
N	185 483

[a] All models were adjusted for age, sex, educational attainment, and smoking status.
[b] Alcohol consumption was categorized as light (>0–<5 g/day, reference), moderate (≥5–<15 g/day), heavy (≥15 g/day), former, and never drinkers.
[c] *N* is the number of study participants included in each model.

could influence subsequent change through mechanisms beyond physiological continuity. However, one could also argue that baseline HbA1c influences follow-up HbA1c only through physiological continuity, reflecting persistence of the same underlying metabolic processes over time. Distinguishing between these mechanisms is challenging in observational studies, making it difficult to determine whether the effect estimands should be expected to coincide when examining changes for cardiometabolic markers such as those studied here.

Our longitudinal findings showed generally small associations, primarily among former drinkers, who had lower 5-year TG change and higher SBP, DBP, and HDL-C changes compared with light drinkers; heavy drinkers additionally had lower DBP change. The associations observed among former drinkers may partly reflect the sick-quitter effect, where individuals discontinue alcohol consumption in response to previously elevated cardiometabolic markers or other health concerns. Previous observational findings have been mixed, with reduction in alcohol consumption positively associated with changes in HDL-C but not TG or blood pressure in one study [31], while another reported increases in SBP and DBP with increasing alcohol consumption [32]. Experimental evidence provides additional context: alcohol consumption increased HDL-C but had no effect on TG in a meta-analysis of intervention studies [33], while a meta-analysis of randomized trials found no effect of light-to-moderate alcohol consumption on HbA1c among individuals with diabetes [34]. Randomized trials of alcohol reduction also showed reductions in both SBP and DBP [35].

While cross-sectional analyses showed stronger between-person differences in markers by drinking group, these contrasts were not reflected longitudinally. Cross-sectional associations may reflect differences accumulated over longer periods, but may also be influenced by reverse causation, whereas our longitudinal analyses captured changes over a shorter, 5-year interval. The smaller longitudinal associations despite cross-sectional differences could suggest that some alcohol-related metabolic differences developed earlier in life and were maintained through midlife.

Our cross-sectional results are in line with previous observations of higher BP [36–39] and HDL-C [18, 31] and lower HbA1c [20, 40, 41] among drinkers. For TG, moderate drinkers had lower levels and never drinkers higher compared to light. This is broadly consistent with prior studies reporting an inverse relationship between alcohol and TG [42], or describing a J-shaped association [14, 32, 42].

Results from the models using the follow-up value of each indicator as the outcome and mixed-effects models were generally consistent with those from the cross-sectional analysis. Importantly, because our mixed-effects models did not include an alcohol × time interaction, the estimates should be interpreted as average level differences across the two measurements rather than differences in change over time. Inclusion of such an interaction with only two time points would instead estimate group differences in change over the 5-year interval, similar to the change-score model. This distinction is important and illustrated in the literature where similar terms (e.g. “weight change”) are sometimes used to describe analyses based on different modeling strategies [43, 44], highlighting the importance of model specification and interpretation.

This study is, to our knowledge, the first to apply and compare three longitudinal modeling approaches within a single observational framework examining cardiometabolic health indicators. The use of high-quality biomarker data collected at two time points from a large, well-characterized cohort enhances our findings’ validity. The study, however, has limitations. Because alcohol consumption was assessed only at baseline, changes in drinking behavior over the 5-year period may have influenced the estimated associations. Moreover, follow-up data for some markers were incomplete for a substantial proportion of participants, potentially introducing selection bias.

Table 3 Longitudinal analysis for the effect of alcohol consumption at baseline on cardiometabolic health markers over 5 years.

Method Variable	Change-score Estimate (95% CI)[b]	Change-score adjusted for baseline Estimate (95% CI)[b]	Oldham's Estimate (95% CI)[b]	Oldham's test[a] Correlation (*P*-value)	Variance ratio test Statistic (*P*-value)
TG (mmol/L) Average 5-year change: 0.01				−0.060 (<.001)	17.19 (<.001)
Light drinkers[c]	Ref	Ref	Ref		
Moderate drinkers	0.01 (−0.01 to 0.02)	−0.02 (−0.04 to −0.01)	0.00 (−0.01 to 0.02)		
Heavy drinkers	−0.01 (−0.03 to 0.02)	−0.02 (−0.04 to 0.00)	−0.01 (−0.03 to 0.02)		
Former drinkers	−0.09 (−0.14 to −0.05)	−0.10 (−0.13 to −0.07)	−0.10 (−0.14 to −0.05)		
Never drinkers	−0.01 (−0.05 to 0.04)	0.02 (−0.02 to 0.06)	0.00 (−0.05 to 0.04)		
N[d]	79 054	79 054	79 054		
SBP (mmHg) Average 5-year change: 0.35				0.015 (<.001)	−5.41 (<.001)
Light drinkers	Ref	Ref	Ref		
Moderate drinkers	0.00 (−0.20 to 0.21)	0.16 (−0.02 to 0.34)	−0.01 (−0.21 to 0.19)		
Heavy drinkers	−0.17 (−0.40 to 0.06)	0.57 (0.36 to 0.77)	−0.23 (−0.46 to 0.01)		
Former drinkers	0.73 (0.25 to 1.20)	0.01 (−0.42 to 0.44)	0.77 (0.29 to 1.24)		
Never drinkers	0.44 (−0.02 to 0.90)[e]	−0.02 (−0.43 to 0.40)	0.47 (0.01 to 0.92)		
N	133 157	133 157	133 157		
DBP (mmHg) Average 5-year change: −0.69				−0.013 (<.001)	4.82 (<.001)
Light drinkers	Ref	Ref	Ref		
Moderate drinkers	0.07 (−0.05 to 0.20)	0.15 (0.04 to 0.26)	0.07 (−0.05 to 0.20)		
Heavy drinkers	−0.15 (−0.30 to −0.01)	0.30 (0.18 to 0.43)	−0.17 (−0.31 to −0.03)		
Former drinkers	0.33 (0.04 to 0.62)	−0.16 (−0.42 to 0.09)	0.34 (0.05 to 0.63)		
Never drinkers	0.27 (−0.01 to 0.54)[e]	0.04 (−0.21 to 0.29)	0.27 (0.00 to 0.55)		
N	133 151	133 151	133 151		
HDL-C (mmol/L) Average 5-year change: 0.02				0.017 (<.001)	−4.84 (<.001)
Light drinkers	Ref	Ref	Ref		
Moderate drinkers	0.00 (−0.01 to 0.00)	0.02 (0.01 to 0.02)	−0.01 (−0.01 to 0.00)		
Heavy drinkers	0.00 (−0.01 to 0.00)	0.03 (0.03 to 0.04)	−0.01 (−0.01 to 0.00)		
Former drinkers	0.02 (0.01 to 0.03)	0.00 (0.00 to 0.01)	0.02 (0.01 to 0.03)		
Never drinkers	0.00 (−0.01 to 0.01)[e]	−0.01 (−0.02 to 0.00)	0.01 (0.00 to 0.02)		
N	80 999	80 999	80 999		
HbA1c (mmol/mol) Average 5-year change: 1.36				0.10 (<.001)	−30.13 (<.001)
Light drinkers	Ref	Ref	Ref		
Moderate drinkers	−0.03 (−0.10 to 0.04)	−0.19 (−0.26 to −0.13)	0.03 (−0.04 to 0.10)		
Heavy drinkers	−0.05 (−0.14 to 0.03)	−0.30 (−0.38 to −0.22)	0.04 (−0.04 to 0.13)		
Former drinkers	0.03 (−0.17 to 0.22)	0.10 (0.04 to 0.17)	−0.04 (−0.23 to 0.15)		
Never drinkers	0.02 (−0.16 to 0.21)	0.23 (0.05 to 0.41)	−0.06 (−0.25 to 0.13)		
N	81 162	81 162	81 162		

[a] Oldham's test corresponds to the Pearson correlation between change and the average of baseline and follow-up outcome values.
[b] Estimates were adjusted for age, sex, educational attainment, and smoking status.
[c] Alcohol consumption was categorized as light (>0–<5 g/day, reference), moderate (≥5–<15 g/day), heavy (≥15 g/day), former, and never drinkers.
[d] *N* is the number of study participants included in each model.
[e] The small discrepancy between the change-score and Oldham's model disappears when we adjust for BMI (Supplementary Table B).

Additionally, changes in medication use during follow-up, including the initiation of antihypertensive, lipid-lowering, or glucose-lowering treatment, may have contributed to changes in cardiometabolic markers over time. Measurement error in the outcome variables remains a potential source of bias as in any observational study, regardless of the modeling approach used. Finally, using only two time points limited our ability to model non-linear trajectories or temporal patterns.

Conclusion

This study highlights the importance of model choice in longitudinal observational analyses. Change-score and Oldham's models produced highly consistent results across all five cardiometabolic markers, whereas the change-score adjusted for baseline altered several associations including their presence and direction. Based on the change-score models, former drinkers had lower 5-year TG change and higher SBP, DBP, and HDL-C changes compared with light drinkers, while heavy drinkers had lower DBP change. The longitudinal findings did not fully reflect the stronger cross-sectional differences in cardiometabolic markers. When the exposure precedes the baseline value of the outcome, our findings demonstrate that baseline adjustment can alter the magnitude and interpretation of longitudinal associations, even when the observed effects are small.

Ethics approval

The German National Cohort (NAKO) is performed with the approval of the relevant local ethics committees and is in accordance with national law and with the Declaration of Helsinki of 1975 (in the current, revised version). Written informed consent was obtained from all participants.

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Author contributions

Martina Bouka, Katharina Nimptsch, Solange Gonzalez Chiappe, Tobias Pischon (Conceptualization), Katharina Nimptsch, Tobias Pischon (Data curation), Martina Bouka, Katharina Nimptsch, Ulrike Grittner, Tobias Pischon (Methodology), Martina Bouka, Katharina Nimptsch, Tobias Pischon (Formal analysis and investigation), Martina Bouka (Writing—original draft preparation), Katharina Nimptsch, Ulrike Grittner, Solange Gonzalez Chiappe, Gertraud Maskarinec, Annette Peters, Claudia Meinke-Franze, Hansjörg Baurecht, Heiko Becher, Henry Völtzke, Hermann Brenner, Isti Rodiah, Lilian Krist, Michael Leitzmann, Nadia Obi, Peggy Sekula, Rafael Mikolajczyk, Stefan N. Willich, Tobias Pischon (Writing—review & editing), Tobias Pischon (Funding acquisition), Tobias Pischon (Resources), and Katharina Nimptsch, Tobias Pischon (Supervision)

Supplementary material

Supplementary material is available at IJE online.

Conflicts of interest

None declared.

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Data availability

The data underlying this article were accessed from the German National Cohort (NAKO Gesundheitsstudie). Due to ethical and data protection restrictions, the data cannot be shared publicly. NAKO data can be obtained via an electronic application portal www.nako.de/transferhub based on a written request and subject to approval by the NAKO Data Use and Access Committee. The R code underlying this article is provided as Supplementary Material in the form of R Markdown (.Rmd) files.

Use of artificial intelligence (AI) tools

ChatGPT (OpenAI) was used to improve readability and English grammar. All scientific content and interpretations remain the responsibility of the authors.

Reporting guidelines

This study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for observational studies (Supplementary Material 2).

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