Alcohol intake and cardiovascular disease and mortality: the role of pre-existing disease

I H M Friesema, P J Zwietering, M Y Veenstra, J A Knottnerus, H F L Garretsen, P H H M Lemmens

See end of article for
authors' affiliations
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Correspondence to:
I H M Friesema, RIVM,
pb75, PB 1, 3720 BA
Bilthoven, The Netherlands;
Ingrid.friesema@rivm.nl

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Objectives: Pre-existing conditions have been postulated as possible causes of the J-shaped relationship between alcohol intake and cardiovascular disease. Two research questions have been addressed in this paper. First, whether never drinkers and former drinkers differ from moderate drinkers in terms of health, and if so, which health problems contribute to this difference. Second, whether the U-shaped relationship between current alcohol intake and cardiovascular disease or all-cause mortality could in part be explained by difference in pre-existing disease burden.

Design, setting and participants: A prospective case-cohort, the Lifestyle and Health Study, consisting of 16 210 men and women aged between 45 and 70 years. Alcohol intake and risk factors were assessed at baseline with a self-administered questionnaire. Medical information was obtained from general practitioners. Cardiovascular events and mortality were followed for a period of 5 years (1996–2001).

Main results: Never drinkers and former drinkers were less healthy than moderate drinkers. They rated their health more often as poor, and often had more diseases, such as cardiovascular disease, diabetes, and also alcohol-related diseases. The difference in disease burden did not change the observed relationship between alcohol intake and cardiovascular events, and only partially changed the U-shaped relationship between alcohol intake and all-cause mortality.

Conclusions: The found difference in health between never drinkers and former drinkers compared with moderate drinkers appeared to be only a partial explanation of the observed relationships between alcohol intake and cardiovascular disease, and between alcohol intake and all-cause mortality.

Numerous studies have demonstrated a U-shaped or J-shaped association between alcohol intake and cardiovascular disease,[1][2] and between alcohol intake and all-cause mortality.[1][3] In these studies, both non-drinkers and heavy drinkers appear to have higher morbidity and mortality rates than light and moderate drinkers. In most studies, the group of non-drinkers consists of lifelong abstainers and ex-drinkers, and in some cases, occasional drinkers. Despite this heterogeneity, the group of non-drinkers is often used as a reference group, which possibly causes overestimation of the potential beneficial effects for moderate drinkers.[2] Furthermore, non-drinkers, particularly former drinkers, seem to be less healthy than moderate drinkers.[4–6] This difference in health could have an impact on the relationship between alcohol intake and cardiovascular disease, causing an overestimation of this relationship. Subjective health has been related to alcohol intake, in which non-drinkers more often reported poor subjective health than moderate drinkers.[7][8] Poor subjective health has also been related to higher risk of all-cause and cardiovascular disease mortality.[9–12]

Health or health problems are important motives for abstaining.[13] Possible reasons behind these motives are medications contradicting the use of alcohol, advice of abstinence or moderation after being diagnosed with a specific disease, such as kidney problems, or with alcohol-related diseases such as liver problems. Furthermore, diseases starting early in life—for example, congenital diseases or chronic diseases—could be an individual reason to abstain from alcohol. Shaper *et al*[14] have examined the influence of pre-existing cardiovascular-related diseases on the relationship between alcohol intake and mortality due to cardiovascular disease. They concluded that the observed relationship seemed to be produced by pre-existing disease. Most of the studies attempt to avoid the bias due to pre-existing disease by excluding individuals with pre-existing cardiovascular disease, diabetes and/or cancer, or by statistically adjusting for these diseases.

This study addresses two research questions. First, whether never drinkers and former drinkers differ from moderate drinkers in terms of health, and if so, which health problems contribute to this difference. Second, whether the U-shaped relationship between current alcohol intake and cardiovascular disease or all-cause mortality can be explained by a difference in pre-existing disease burden.

METHODS

Population and design

The Lifestyle and Health Study (Leefstijl en Gezondheid Onderzoek, LEGO) is a prospective cohort study on alcohol intake and cardiovascular disease. The cohort was established in June 1996 using databases from 34 general practices. In the Netherlands, general practitioners (GPs) have a central role in health care by arranging for everyone to be registered with a primary practice.[15][16] Practices were recruited by Regional Services for Public Health. For practical reasons, participation of practices was restricted to two regions in the southeastern and western part of the Netherlands.

All men and women aged between 45 and 70 years registered with these 34 practices received a questionnaire. Terminally ill patients, patients with severe dementia, mentally disabled patients and institutionalised patients were excluded in advance. A total of 16 210 subjects (51.7%) responded to the mailed questionnaire. Informed consent was obtained in a letter presenting the questionnaire. The participants were

followed up until June 2001 and received a follow-up questionnaire each year between 1997 and 2000.

The study design was approved by the review committee of the Registration Network Family Practices of the University of Maastricht, Maastricht, The Netherlands. For reasons of efficiency, a case-cohort approach was applied, involving a selection of a random sample at baseline.[17] [18] This sample, further referred to as subcohort (n = 3253), was used in the analyses as the control group.

Alcohol intake

Baseline measurement consisted of a detailed self-administered questionnaire assessing, among others, the main cardiovascular risk factors. Current alcohol intake was assessed using a Weekly Recall and a Quantity–Frequency form about last year's consumption (QF-last-year). The Weekly Recall assessed actual intake per day in the week before baseline separately for beer, wine and spirits. Actual weekly consumption was calculated by adding up all drinks. The usual consumption in the year before baseline was ascertained with the QF-last-year by questions about usual quantity and frequency, again separately for beer, wine and spirits. The beverage-specific weekly consumptions were added up to total weekly consumption. Lifetime abstaining was defined as no drinks during lifetime and was derived from the Lifetime Drinking History questionnaire. The Lifetime Drinking History questionnaire is a self-administered questionnaire about alcohol intake since the first glass drunk,[19] [20] and was also assessed at baseline. Subjects who drunk during lifetime, but did not drink according to the QF-last-year were defined as former drinkers.

Current alcohol intake was distinguished into seven categories: never drinkers; former drinkers; <1 glass/week; 1–6.9 glasses/week; 7–14.9 glasses/week (moderate drinkers); 15–28 glasses/week; >28 glasses/week. For the Weekly Recall, the category of drinkers of <1 glass/week was determined with the QF-last-year. In the Netherlands, one glass of alcohol approximates 10 g of pure alcohol.

Pre-existing disease and subjective health

Medical information was obtained by GPs who filed all major health problems of the past and of the follow-up period of their patients on problem lists.[21] Categorisation of the health problems was done using International Classification of Primary Care (ICPC) codes.[22] The ICPC codes are classified under 17 chapters. In different analyses, several groups of diseases were formed. Diseases were included only if date of diagnosis was before the start of the study. First, broad categories of health problems were selected, using the categorisation in chapters of the ICPC. In each chapter, ICPC codes between 70 and 99 represent diagnoses and diseases. Each chapter was analysed using these codes, except chapter W (pregnancy & family planning) and codes 95, 96 and 97 in chapter A (general and unspecified diseases)). The codes between 01 and 29 are assigned to symptoms and complaints. This group of codes was analysed for chapters D (digestive problems), L (musculoskeletal problems), N (neurological problems) and P (psychological problems). Besides the broad categories, more specific categories of diseases were analysed, based on known risk factors for cardiovascular disease and possible motives for abstaining (box 1).

Subjective health was derived from the self-administered questionnaire. Respondents were asked whether their health was very good, good, moderate, poor or very poor. In the analyses, these five options were reduced to two categories comparing (very) good health with moderate and (very) poor health, the latter further referred as poor subjective health.

End points

Two groups of end points were distinguished: cardiovascular events, comprising fatal and non-fatal events, and all-cause mortality. Cardiovascular events, occurring in the period from July 1996 to June 2001, were derived from the problem lists and were reported by the GPs. Cardiovascular events on the problem lists were specified as coronary heart diseases (K74 or K75 or K76), heart failure (K77) and/or stroke (K89 or K90). All new myocardial infarctions and all deaths were also reported by the GPs to the research team as soon as possible after presentation. Cause of death was reported by the GP using nine main categories: myocardial infarction; other cardiac deaths; stroke; other vascular deaths; cancer; infection or autoimmune diseases; violence or accident; suicide; other or unknown causes. Fatal myocardial infarctions, other cardiac deaths, fatal stroke and other vascular deaths were also included in the cardiovascular events. Discrepancies between problem lists and reports were traced and resolved with the GPs.

Data analysis

First, current alcohol intake in relation to pre-existing diseases and subjective health was analysed using logistic regression. Moderate drinkers were compared with never drinkers and former drinkers for each defined group of diseases. Analyses were done separately for men and women using both alcohol questionnaires.

Second, the relationships between current alcohol intake, on the one hand, and cardiovascular events, and all-cause mortality respectively, on the other, were analysed with three different models using Cox regression. The Cox regression model was adapted for the case-cohort design by defining the entry time of subjects into the analysis as just before the event for all cases outside the subcohort. Standard errors (SE) of the estimated parameters were estimated using the robust Huber–White sandwich estimator to account for additional variance introduced by sampling from the cohort.[23] All analyses were done separately for men and women, and for both QF-last-year and Weekly Recall. All models were adjusted for age (continuous), region (southeast/west), pack-years (non-smokers and categorisation of number of pack-years in quartiles), body mass index (quintiles), fat intake (quintiles), physical activity (quintiles), education (7 categories) and income (5 categories). The classification into quartiles or quintiles was done using the distribution in the subcohort.

First model included the above-mentioned covariates, but did not take pre-existing disease into account. In the second model, persons who defined their health as poor were excluded (exclusion 1). The last model comprised healthy subjects only (exclusion 2). Healthy subjects were defined as persons free of the pre-existing diseases found to be related to current alcohol intake (p<0.05) in the logistic regression and who rated their health as (very) good.

The total cohort consisted of 16 210 persons, of whom 330 men and 204 women died, and 679 men and 397 women had a cardiovascular event. These subjects with an end point, and the subcohort (n = 3135), were included in the analysis. Cases and subcohort members were excluded in case of missing medical data (n = 229) or missing data on alcohol intake (n = 80). This left a total of 2984 subcohort members, 323 men and 200 women who died, and 675 men and 395 women who had a cardiovascular event, with some cases also belonging to the subcohort.

RESULTS

In the subcohort, 73.6% of the men and 57.6% of the women currently drank alcohol according to the Weekly Recall and, respectively, 81.5% and 56.2% had at least drunk once a week

Box 1 Summary of included groups of pre-existing disease

- Known risk factors for cardiovascular disease

  – pre-existing cardiovascular disease, hypertension, diabetes mellitus

- Alcohol-related diseases

  – total group of alcohol-related diseases, liver problems and diseases, oesophagus and stomach problems and diseases, pancreas problems and diseases

- Medication use in case of

  – epilepsy, psychosis, depression, lung problems and diseases, suffering from side effects of medication without specification

- Possible advice about alcohol intake

  – cancer, anxiety for getting an illness, generalised fear, functional somatic syndromes, visual handicaps, vertiginous syndromes and vertigo/dizziness, neuropathy, vitamin deficiency and other nutritional diseases, gout, kidney problems and diseases, prostate problems and diseases

- Chronic diseases

  – backache, osteoarthritis and rheumatoid arthritis, headache, thyroid gland problems and diseases, congenital anomalies and influential diseases experienced before the age of 20 years

according to the QF-last-year. 10.6% of the men and 3.2% of the women drunk on average >28 glasses/week, and 10.5% of the men and 1.5% of the women drunk this amount in the week before baseline. The QF-last-year was available for 1961 men and 1713 women, combining subcohort and cases. Of these, 472 (24.1%) men and 254 (14.8%) women drank 7–14.9 glasses/week. Actual intake in the week before the baseline was available for 1762 men of whom 365 (20.7%) were moderate drinkers, and 1501 women of whom 225 (15%) drank moderately.

Tables 1 (men) and 2 (women) present the diseases and complaints found to be significantly related to never drinkers and/or former drinkers. Pancreas problems and diseases, and vitamin deficiency and other diseases related to nutritional deficiencies could not be analysed due to very few cases.

In men, never drinkers were more often diagnosed with neuropathy, visual handicaps, diabetes mellitus, oesophagus and stomach problems and diseases, and diseases of the genital system than moderate drinkers. Remarkably, never drinkers also had alcohol-related diseases more often. Both never drinkers and former drinkers rated their health more often as poor than the moderate drinkers. Former drinkers more often had circulatory diseases, especially cardiovascular diseases, endocrine and metabolic diseases especially diabetes mellitus, and alcohol-related diseases than moderate drinkers. Neurological diseases and psychological problems and diseases, such as depression, were also more common among former drinkers compared to moderate drinkers. Differences in results between current alcohol intake measured with QF-last-year and Weekly Recall were overall small. Differences in significance were only found for former drinkers—namely, for general and unspecified diseases, psychological problems, depression

and epilepsy. The other groups of pre-existing disease were not significantly related to current alcohol intake.

In women, the largest differences for both never drinkers and former drinkers compared with moderate drinkers were found in subjective health and diabetes mellitus. Never drinkers also had more often digestive diseases, cardiovascular diseases, hypertension and, similar to the men, alcohol-related diseases. Less-pronounced differences were found for digestive problems, psychological diseases, functional somatic syndromes, and oesophagus and stomach problems and diseases. Former drinkers were more often diagnosed with circulatory, especially cardiovascular diseases, and digestive diseases than moderate drinkers. Neurological problems were found to be significantly more common among never drinkers and former drinkers when using the QF-last-year, but not when using the Weekly Recall. The opposite was found for depression for both never and former drinkers, and alcohol-related diseases, and thyroid gland problems and diseases for former drinkers only.

Tables 3 and 4 give the results for the relationship between current alcohol intake and all-cause mortality, and current alcohol intake and cardiovascular events with and without exclusion of non-healthy subjects for, respectively, men and women. Without exclusions of non-healthy subjects, both male and female drinkers appear to have lower risks of all-cause mortality and cardiovascular events than never drinkers. Excluding men with poor subjective health did not appear to reveal differences in point estimates for drinkers, as excluding all men with one or more pre-existing diseases seemed to reduce the difference in all-cause mortality between drinking and abstaining men compared to the total group of men. Healthy male former and occasional drinkers seemed to have higher risk of all-cause mortality compared with never drinkers than in the total group of men, when using the Weekly Recall. Exclusion of men reporting poor health did not seem to have much effect on the relationship between alcohol intake and cardiovascular disease. The relationship between current alcohol intake and cardiovascular events seemed to become smaller when excluding non-healthy men (exclusion 2). Excluding women with poor subjective health led to lower point estimates for all-cause mortality for former drinkers compared with the total group. Exclusion of non-healthy women (exclusion 2) appeared to moderate the risk of all-cause mortality for drinkers. The relationship between current alcohol intake and cardiovascular events for women was linear instead of U-shaped. Healthy female former drinkers appear to have a lower risk of cardiovascular events compared with never drinkers, which was seen less in the total group of women. Both exclusions did not seem to affect the point estimates for drinkers.

DISCUSSION

This study showed that both male and female never drinkers and former drinkers were less healthy and rated their subjective health more often as poor than moderate drinkers. Exclusion of subjects with one or more of these health problems related to alcohol intake seemed to lead to a smaller difference in risk of all-cause mortality between never drinkers and moderate drinkers. For cardiovascular events, the differences between healthy subjects and the total group were less clear.

Subjective health is an indicator of the health status of the respondent. In this study, never drinkers and former drinkers more often reported poor subjective health than moderate drinkers. Previous studies have also observed that more often non-drinkers have poor subjective health than drinkers, the pattern of which can be described as J-shaped.[7][8][24] Furthermore, poor subjective health has been related to a higher risk of all-cause mortality and cardiovascular disease.[9–12]

Table 1 ORs (95% CI) for health problems comparing never drinkers and former drinkers with moderate drinkers (reference group) for men

	QF-last-year		Weekly recall	
	Never drinkers	Former drinkers	Never drinkers	Former drinkers
	n = 39	n = 218	n = 39	n = 184
Poor subjective health	2.19 (1.11 to 4.34)	3.53 (2.46 to 5.07)	2.16 (1.08 to 4.34)	4.23 (2.84 to 6.31)
(A) General and unspecified diseases	0.92 (0.21 to 4.12)	2.03 (1.11 to 3.70)	0.74 (0.17 to 3.28)	1.48 (0.79 to 2.79)
(K) Circulatory diseases	1.49 (0.76 to 2.90)	1.74 (1.25 to 2.44)	1.48 (0.75 to 2.92)	1.91 (1.32 to 2.78)
(N) Neurological diseases	0.88 (0.20 to 3.90)	2.08 (1.15 to 3.76)	0.89 (0.20 to 4.01)	2.03 (1.05 to 3.93)
(P) Psychological problems	0.33 (0.04 to 2.51)	1.65 (0.96 to 2.85)	0.40 (0.05 to 3.03)	2.18 (1.16 to 4.10)
(P) Psychological diseases	1.73 (0.57 to 5.24)	1.86 (1.04 to 3.35)	2.24 (0.71 to 7.06)	2.55 (1.28 to 5.07)
(T) Endocrine and metabolic diseases	1.60 (0.75 to 3.43)	1.90 (1.30 to 2.78)	1.83 (0.84 to 3.96)	2.04 (1.33 to 3.14)
(Y) Diseases of male genital system	2.60 (1.05 to 6.46)	1.08 (0.58 to 2.00)	2.65 (1.04 to 6.74)	1.08 (0.55 to 2.13)
Alcohol-related diseases	2.09 (1.03 to 4.24)	1.54 (1.05 to 2.24)	2.16 (1.05 to 4.45)	1.72 (1.13 to 2.61)
Oesophagus/stomach problems and diseases	2.85 (1.25 to 6.50)	1.28 (0.75 to 2.19)	3.39 (1.43 to 8.05)	1.59 (0.87 to 2.89)
Visually handicapped	7.75 (1.33 to 45.07)	1.06 (0.19 to 5.90)	11.05 (1.48 to 82.44)	1.86 (0.26 to 13.42)
Cardiovascular diseases	1.38 (0.63 to 3.01)	2.22 (1.50 to 3.26)	1.36 (0.61 to 3.00)	2.51 (1.65 to 3.83)
Epilepsy	*	11.04 (1.27 to 95.82)	*	5.31 (0.55 to 51.72)
Neuropathy	9.96 (1.32 to 75.10)	3.82 (0.69 to 21.17)	*	*
Depression	2.06 (0.44 to 9.64)	2.13 (0.92 to 4.93)	3.54 (0.66 to 19.07)	3.84 (1.26 to 11.70)
Diabetes mellitus	3.29 (1.13 to 9.55)	3.17 (1.69 to 5.95)	3.01 (1.03 to 8.78)	2.91 (1.49 to 5.69)

QF-last-year, quantity–frequency form about last year's consumption.
*Very few cases.

In this study, the effects of exclusion of subjects with poor subjective health from the analyses were minimal on the relationships between alcohol intake and cardiovascular events, and all-cause mortality. The U-shaped curve between alcohol intake and all-cause mortality, or cardiovascular events therefore, could not be explained by subjective health.

The relationship between alcohol intake and health problems has been studied before.[4–6] The type and definition of the health problems between the studies differ and no clear associations could be seen. Nevertheless, digestive problems, cardiovascular problems and diabetes are often reported to occur more among non-drinkers than drinkers. Although these relationships were found in this and other studies, it is not clear what appeared first. The health problems could have led subjects to stop drinking or even stay as a never drinker. In this study, no relationship between congenital diseases and diseases diagnosed before the age of 20 years and alcohol intake was found. It could indicate that health problems do not influence reasons for being a never drinker. Another possibility is selection bias

with respect to chronically ill persons not participating in the study. On the other hand, abstaining could also have led to health problems, which would confirm the beneficial effect of alcohol intake. This has, for example, been stated for cardiovascular disease and diabetes. Finally, heavy drinking can cause serious health problems, such as liver diseases, with subjects consequently becoming non-drinkers. However, prospective observational studies can only indicate a certain direction, but cannot demonstrate causality.

When comparing the three different models specified in this study, one has to conclude that pre-existing disease does affect the risk estimates regarding the relationship between alcohol intake and all-cause mortality, but not regarding the relationship between alcohol intake and cardiovascular events. The effect of pre-existing disease on the relationship between alcohol intake and all-cause mortality is, however, not strong enough to explain the U-shaped curve of this relationship. This contradicts the findings of Shaper et al[14] who suggested that relationships between alcohol intake and mortality could be

Table 2 ORs (95% CI) for health problems comparing never and former drinkers with moderate drinkers (reference group) for women

	QF-last-year		Weekly recall	
	Never drinkers	Former drinkers	Never drinkers	Former drinkers
	n = 203	n = 270	n = 203	n = 179
Poor subjective health	3.42 (2.20 to 5.30)	3.18 (2.12 to 4.76)	3.64 (2.31 to 5.74)	3.77 (2.39 to 5.95)
(D) Digestive problems	2.71 (0.96 to 7.69)	1.60 (0.61 to 4.21)	4.88 (1.14 to 16.88)	2.50 (0.67 to 9.31)
(D) Digestive diseases	2.13 (1.32 to 3.43)	1.61 (1.03 to 2.50)	1.83 (1.14 to 2.94)	1.67 (1.03 to 2.72)
(K) Circulatory diseases	1.49 (0.99 to 2.26)	1.49 (1.02 to 2.17)	1.48 (0.97 to 2.26)	1.60 (1.04 to 2.45)
(N) Neurological problems	3.78 (1.06 to 13.52)	3.17 (1.02 to 9.90)	2.09 (0.68 to 6.44)	2.33 (0.81 to 6.73)
(N) Neurological diseases	1.44 (0.72 to 2.87)	1.81 (1.00 to 3.27)	0.97 (0.50 to 1.90)	1.54 (0.83 to 2.88)
(P) Psychological diseases	2.00 (0.99 to 4.03)	1.57 (0.81 to 3.06)	2.84 (1.29 to 6.26)	3.09 (1.41 to 6.78)
(T) Endocrine and metabolic diseases	1.88 (1.21 to 2.92)	1.60 (1.07 to 2.41)	2.48 (1.55 to 3.98)	2.22 (1.38 to 3.58)
Alcohol-related diseases	1.67 (1.07 to 2.61)	1.36 (0.89 to 2.07)	1.94 (1.22 to 3.08)	1.78 (1.11 to 2.86)
Functional somatic syndromes	2.56 (1.14 to 5.76)	1.64 (0.76 to 3.56)	2.00 (0.91 to 4.40)	1.59 (0.70 to 3.65)
Oesophagus/stomach problems and diseases	3.37 (1.35 to 8.41)	1.36 (0.53 to 3.44)	2.11 (0.92 to 4.85)	1.37 (0.56 to 3.38)
Cardiovascular diseases	1.96 (1.03 to 3.72)	2.40 (1.32 to 4.39)	2.19 (1.13 to 4.27)	2.72 (1.41 to 5.26)
Hypertension	1.70 (1.04 to 2.78)	1.68 (1.05 to 2.69)	1.95 (1.16 to 3.28)	2.07 (1.22 to 3.53)
Depression	2.06 (0.82 to 5.17)	2.08 (0.88 to 4.88)	3.49 (1.10 to 11.09)	5.03 (1.64 to 15.46)
Thyroid gland problems and diseases	0.86 (0.40 to 1.83)	1.27 (0.67 to 2.40)	1.52 (0.65 to 3.57)	2.21 (1.01 to 4.83)
Diabetes mellitus	6.92 (2.32 to 20.64)	7.05 (2.43 to 20.50)	6.85 (2.29 to 20.44)	6.74 (2.25 to 20.18)

QF-last-year, quantity–frequency form about last year's consumption.

Table 3 HRs (95% CI) for alcohol intake and all-cause mortality, or cardiovascular events without and with exclusion of non-healthy men

	Cases/n	Never drinkers	Former drinkers	Drinkers (in glasses/week)				
				<1	1–6.9	7–14.9	15–28	>28
All-cause mortality								
Weekly Recall, no exclusions*	275/1413	1	0.91 (0.33 to 2.51)	2.03 (0.76 to 5.39)	0.12 (0.05 to 0.34)	0.16 (0.06 to 0.43)	0.29 (0.11 to 0.79)	0.24 (0.08 to 0.73)
Weekly Recall, exclusion 1†	148/1051	1	1.74 (0.43–6.98)	2.20 (0.60 to 8.05)	0.15 (0.04 to 0.56)	0.17 (0.04 to 0.68)	0.23 (0.06 to 0.88)	0.31 (0.07 to 1.31)
Weekly Recall, exclusion 2‡	68/568	1	3.36 (0.64 to 17.73)	19.37 (3.52 to 106.73)	0.28 (0.05 to 1.51)	0.80 (0.16 to 4.01)	1.53 (0.29 to 8.25)	0.93 (0.14 to 5.93)
QF-last-year, no exclusions*	287/1610	1	0.90 (0.33 to 2.48)	0.54 (0.19 to 1.56)	0.32 (0.12 to 0.85)	0.34 (0.13 to 0.91)	0.33 (0.12 to 0.92)	0.45 (0.15 to 1.31)
QF-last-year, exclusion 1†	157/1223	1	1.56 (0.40 to 6.08)	0.81 (0.20 to 3.20)	0.35 (0.10 to 1.24)	0.48 (0.13 to 1.75)	0.42 (0.11 to 1.58)	0.53 (0.12 to 2.31)
QF-last-year, exclusion 2‡	75/677	1	0.78 (0.09 to 6.47)	0.73 (0.08 to 6.58)	0.50 (0.07 to 3.71)	0.49 (0.06 to 3.78)	0.35 (0.04 to 3.15)	1.05 (0.12 to 9.15)
All cardiovascular events								
Weekly Recall, no exclusions*	577/1648	1	1.44 (0.60 to 3.47)	3.23 (1.37 to 7.59)	0.32 (0.14 to 0.74)	0.40 (0.17 to 0.94)	0.38 (0.16 to 0.91)	0.50 (0.21 to 1.22)
Weekly Recall, exclusion 1†	363/1220	1	2.17 (0.69 to 6.80)	3.22 (1.09 to 9.49)	0.38 (0.13 to 1.11)	0.40 (0.13 to 1.19)	0.38 (0.13 to 1.13)	0.47 (0.15 to 1.46)
Weekly Recall, exclusion 2‡	157/640	1	0.87 (0.18 to 4.31)	4.27 (1.01 to 18.11)	0.21 (0.05 to 0.87)	0.25 (0.06 to 1.02)	0.31 (0.07 to 1.33)	0.32 (0.07 to 1.38)
QF-last-year, no exclusions*	593/1839	1	1.27 (0.55 to 2.93)	0.78 (0.33 to 1.89)	0.66 (0.29 to 1.47)	0.58 (0.26 to 1.31)	0.58 (0.25 to 1.34)	0.73 (0.31 to 1.72)
QF-last-year, exclusion 1†	376/1387	1	0.71 (0.17 to 3.02)	0.69 (0.16 to 2.97)	0.47 (0.12 to 1.79)	0.42 (0.11 to 1.59)	0.59 (0.15 to 2.32)	0.54 (0.14 to 2.13)
QF-last-year, exclusion 2‡	171/751	1	0.51 (0.12 to 2.19)	0.80 (0.19 to 3.41)	0.40 (0.11 to 1.50)	0.43 (0.11 to 1.59)	0.69 (0.18 to 2.66)	0.52 (0.13 to 2.06)

QF-last-year, Quantity–Frequency form about last year's consumption.
*Adjusted for age, region, pack-years, body mass index, fat intake, physical activity, education and income.
†Exclusion 1: exclusion of subjects with poor subjective health, adjusted for age, region, pack-years, body mass index, fat intake, physical activity, education and income.
‡Exclusion 2: exclusion 1 also with the exclusion of the pre-existing diseases found to be related to alcohol intake.

Table 4 HRs (95% CI) for alcohol intake and all-cause mortality, or cardiovascular events without and with exclusion of non-healthy women

	Cases/n	Never drinkers	Former drinkers	Drinkers of (in glasses/week)				
				<1	1–6.9	7–14.9	15–28	>28
All-cause mortality								
Weekly Recall, no exclusions*	156/1289	1	0.79 (0.44 to 1.41)	1.06 (0.60 to 1.87)	0.10 (0.05 to 0.22)	0.23 (0.11 to 0.48)	0.32 (0.13 to 0.80)	0.66 (0.18 to 2.41)
Weekly Recall, exclusion 1†	81/936	1	0.42 (0.13 to 1.31)	1.41 (0.55 to 3.58)	0.11 (0.04 to 0.31)	0.23 (0.08 to 0.70)	0.25 (0.07 to 0.84)	0.55 (0.09 to 3.42)
Weekly Recall, exclusion 2‡	55/563	1	1.91 (0.61 to 5.92)	1.74 (0.60 to 5.06)	0.26 (0.08 to 0.85)	0.49 (0.13 to 1.80)	0.85 (0.20 to 3.55)	*
QF-last-year, no exclusions*	162/1484	1	0.77 (0.45 to 1.30)	0.38 (0.21 to 0.69)	0.24 (0.13 to 0.45)	0.22 (0.10 to 0.46)	0.33 (0.14 to 0.79)	0.80 (0.33 to 1.93)
QF-last-year, exclusion 1†	84/1092	1	0.46 (0.18 to 1.17)	0.29 (0.12 to 0.73)	0.23 (0.09 to 0.56)	0.19 (0.07 to 0.54)	0.26 (0.08 to 0.82)	0.79 (0.21 to 2.98)
QF-last-year, exclusion 2‡	58/673	1	1.23 (0.41 to 3.68)	0.71 (0.23 to 2.17)	0.65 (0.22 to 1.88)	0.25 (0.06 to 1.06)	0.77 (0.18 to 3.32)	1.16 (0.20 to 6.71)
All cardiovascular events								
Weekly Recall, no exclusions*	309/1416	1	0.81 (0.50 to 1.32)	1.38 (0.90 to 2.11)	0.20 (0.12 to 0.33)	0.19 (0.10 to 0.36)	0.20 (0.08 to 0.45)	0.38 (0.10 to 1.45)
Weekly Recall, exclusion 1†	173/1007	1	1 (0.47 to 2.10)	1.50 (0.82 to 2.77)	0.18 (0.09 to 0.36)	0.19 (0.08 to 0.45)	0.14 (0.05 to 0.42)	0.34 (0.07 to 1.74)
Weekly Recall, exclusion 2‡	88/596	1	0.47 (0.16 to 1.41)	1.76 (0.78 to 3.98)	0.16 (0.06 to 0.40)	0.12 (0.03 to 0.45)	0.27 (0.07 to 0.99)	*
QF-last-year, no exclusions*	329/1622	1	0.77 (0.50 to 1.21)	0.56 (0.36 to 0.89)	0.43 (0.28 to 0.67)	0.37 (0.22 to 0.62)	0.21 (0.09 to 0.48)	0.14 (0.04 to 0.49)
QF-last-year, exclusion 1†	185/1170	1	0.97 (0.50 to 1.90)	0.59 (0.31 to 1.12)	0.43 (0.23 to 0.79)	0.31 (0.15 to 0.65)	0.22 (0.08 to 0.60)	0.16 (0.03 to 0.79)
QF-last-year, exclusion 2‡	96/709	1	0.54 (0.21 to 1.42)	0.50 (0.21 to 1.22)	0.47 (0.21 to 1.06)	0.32 (0.12 to 0.84)	0.30 (0.08 to 1.12)	0.14 (0.01 to 1.57)

QF-last-year, Quantity–Frequency form about last year's consumption.
*Adjusted for age, region, pack-years, body mass index, fat intake, physical activity, education and income.
†Exclusion 1: exclusion of subjects with poor subjective health, adjusted for age, region, pack-years, body mass index, fat intake, physical activity, education and income.
‡Exclusion 2: exclusion 1 also with the exclusion of the pre-existing diseases found to be related to alcohol intake.

What this paper adds

- Potential effects of moderate alcohol drinking have received a lot of attention. It is now a widely held view that moderate drinking protects against coronary heart disease. Nevertheless, this relationship could be produced by pre-existing disease. Impact of pre-existing cardiovascular disease has already been reported. However, other pre-existing diseases could also affect both drinking behaviour and risk of cardiovascular disease.

- Therefore, our study studied the impact of a broader range of pre-existing diseases on alcohol intake, and on the relationships between alcohol intake and cardiovascular events and between alcohol intake and all-cause mortality. Several groups of pre-existing diseases were related to alcohol intake. However, the effect of these pre-existing diseases on both relationships was minimal.

produced by pre-existing disease. However, some differences in model specification could have caused this difference in findings. First the British Regional Heart Study could not separate non-drinkers into never drinkers and former drinkers, which has been done in the present study. In a recent review, combining former and never drinkers appeared to produce misclassification.[25] The studies in which different groups of non-drinkers were separated found no significant all-cause or cardiac benefits. A non-specific group of non-drinkers could enlarge the percentage of individuals with some pre-existing disease in this group. Second, Shaper et al[14] included cardiovascular-related diseases only, whereas a broader range of pre-existing disease was taken into account in this study. Finally, the results of the British Regional Heart Study were adjusted for age, social class and smoking. In this study, the models also included body mass index, fat intake and physical activity.

A potential limitation of the study is the response rate of 51.7%. Therefore, a non-response analyses has been done.[26] Respondents were found to have more coronary heart disease, but non-respondents had a higher mortality risk during follow-up. The death rate in the cohort was somewhat lower compared to the Dutch population.[27] Nevertheless, as almost everyone in The Netherlands is enlisted by a GP, this GP is notified by the hospital, another GP and/or relatives in case of hospitalisation or death of a patient. For alcohol intake, no comparisons could be made. If non-response is linked to alcohol intake, it is most likely that heavy drinkers will be under-represented in the study.

In conclusion, non-drinkers, among them both never drinkers and former drinkers, rate their health more often as poor and more often have several health problems, such as cardiovascular disease, diabetes and alcohol-related diseases. However, these differences in health do not seem to explain the observed U-shaped curve between alcohol intake and cardiovascular events and only partially explain the U-shaped curve between alcohol intake and all-cause mortality.

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Authors' affiliations

I H M Friesema, P H H M Lemmens, Department of Health Care Studies, Division Medical Sociology, Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands
P J Zwietering, J A Knottnerus, Department of General Practice, Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands
M Y Veenstra, Addiction Research Institute, Erasmus University Rotterdam, Rotterdam, The Netherlands
H F L Garretsen, Faculty of Social and Behavioural Sciences, Tilburg University, Tilburg, The Netherlands

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REFERENCES

1 **Beaglehole R**, Jackson R. Alcohol, cardiovascular diseases and all causes of death: a review of the epidemiological evidence. *Drug Alcohol Rev* 1992;**11**:275–90.
2 **Corrao G**, Rubbiati L, Bagnardi V, *et al.* Alcohol and coronary heart disease: a meta-analysis. *Addiction* 2000;**95**:1505–23.
3 **Poikolainen K**. Alcohol and mortality: a review. *J Clin Epidemiol* 1995;**48**:455–65.
4 **Cederfjäll J**, Lidfeldt J, Nerbrand C, *et al.* Alcohol consumption among middle-aged women: a population-based study of Swedish women. The Women's Health in Lund Area (WHILA) study. *Eur Addict Res* 2004;**10**:15–21.
5 **Green CA**, Polen MR. The health and health behaviors of people who do not drink alcohol. *Am J Prev Med* 2001;**21**:298–305.
6 **Tracy JI**, Gorman DM, Leventhal EA. Reports of physical symptoms and alcohol use: findings from a primary health care sample. *Alcohol Alcohol* 1992;**27**:481–91.
7 **Guallar Castillón P**, Rodríguez Artalejo F, Díez Gañán LD, *et al.* Consumption of alcoholic beverages and subjective health in Spain. *J Epidemiol Community Health* 2001;**55**:648–52.
8 **Poikolainen K**, Vartiainen E, Korhonen HJ. Alcohol intake and subjective health. *Am J Epidemiol* 1996;**144**:346–50.
9 **Appels A**, Bosma H, Grabauskas V, *et al.* Self-rated health and mortality in a Lithuanian and a Dutch population. *Soc Sci Med* 1996;**42**:681–9.
10 **Kaplan GA**, Goldberg DE, Everson SA, *et al.* Perceived health status and morbidity and mortality: evidence from the Kuopio ischaemic heart disease risk factor study. *Int J Epidemiol* 1996;**25**:259–65.
11 **Pijls LT**, Feskens EJ, Kromhout D. Self-rated health, mortality, and chronic diseases in elderly men. The Zutphen Study, 1985–1990. *Am J Epidemiol* 1993;**138**:840–8.
12 **Wannamethee G**, Shaper AG. Self-assessment of health status and mortality in middle-aged British men. *Int J Epidemiol* 1991;**20**:239–45.
13 **Graham K**. Alcohol abstention among older adults: reasons for abstaining and characteristics of abstainers. *Addict Res* 1998;**6**:473–87.
14 **Shaper AG**, Wannamethee G, Walker M. Alcohol and mortality in British men: explaining the U-shaped curve. *Lancet* 1988;**2**:1267–73.
15 **Van der Linden MW**, Westert GP, De Bakker DH, *et al. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Klachten en aandoeningen in de bevolking en in de huisartspraktijk.* Utrecht/Bilthoven: NIVEL/RIVM, 2004.
16 **Metsemakers JF**, Hoppener P, Knottnerus JA, *et al.* Computerized health information in The Netherlands: a registration network of family practices. *Br J Gen Pract* 1992;**42**:102–6.
17 **Prentice RL**. A case-cohort design for epidemiologic cohort studies and disease prevention trials. *Biometrika* 1986;**73**:1–11.
18 **Langholz B**, Thomas DC. Nested case-control and case-cohort methods of sampling from a cohort: a critical comparison. *Am J Epidemiol* 1990;**131**:169–76.
19 **Lemmens PH**, Volovics L, Haan YD. Measurement of lifetime exposure to alcohol: data quality of a self-administered questionnaire and impact on risk assessment. *Contemp Drug Probl* 1997;**24**:581–600.
20 **Friesema IHM**, Veenstra MY, Zwietering PJ, *et al.* Measurement of lifetime alcohol intake: utility of a self-administered questionnaire. *Am J Epidemiol* 2004;**159**:809–17.
21 **Sandlow LJ**, Bashook PG. *Problem oriented medical records. Self instruction for practitioners.* Chicago: Michael Reese Hospital and Medical Center, 1978:13–15.
22 **Lamberts H**, Wood M. *ICPC: International Classification of Primary Care.* Oxford: Oxford University Press, 1987.
23 **Lin DY**, Wei LJ. The robust inference for the Cox Proportional Hazards Model. *J Am Stat Assoc* 1989;**84**:1074–8.
24 **Gronbaek M**, Mortensen EL, Mygind K, *et al.* Beer, wine, spirits and subjective health. *J Epidemiol Community Health* 1999;**53**:721–4.
25 **Fillmore KM**, Kerr WC, Stockwell T, *et al.* Moderate alcohol use and reduced mortality risk: systematic error in prospective studies. *Addiction Res Theory* 2006;**14**:101–32.
26 **Veenstra MY**, Friesema IHM, Zwietering PJ, *et al.* Lower prevalence of heart disease but higher mortality risk during follow-up was found among nonrespondents to a cohort study. *J Clin Epidemiol* 2006;**59**:410–18.
27 **Sterfte naar leeftijd, geslacht en burgerlijk staat**. Centraal Bureau voor de Statistiek: http://statline.cbs.nl/StatWeb/ (accessed on 29 Jan 2007).