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**Département de Médecine et Santé Communautaires**

# ALCOHOL USE IN COMMUNITY-DWELLING OLDER PERSONS AGED 65 TO 70 YEARS: CROSS-SECTIONAL AND LONGITUDINAL ASSOCIATION WITH FRAILTY, GAIT PERFORMANCE AND HEALTH CARE USE.

**Thèse de doctorat ès sciences de la vie (PhD)**

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Faculté de biologie et de médecine
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par

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Lausanne, le 21 mars 2016

pour le Doyen
de la Faculté de biologie et de médecine

Prof. Peter Vollenweider

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## RESUME

Plusieurs études montrent qu'une consommation modérée d'alcool a un effet protecteur contre les maladies cardiovasculaires, mais que l'alcool est associé à un risque accru de cancers, d'hypertension et d'accidents, quelle que soit la quantité consommée. Le rapport risque-bénéfice de l'alcool est probablement moins favorable chez les personnes âgées que chez les adultes d'âge moyen, notamment en raison de modifications du métabolisme, de maladies chroniques et de la prise de médicaments, toutes plus fréquentes avec l'âge.

Ce travail décrit la consommation d'alcool chez les participants à l'étude Lausanne cohorte 65+. La plupart des 1564 participants âgés de 65 à 70 ans (58%) rapportaient une consommation dans les limites recommandées pour la santé, soit au maximum 1 verre/jour pour les femmes et 2 verres/jour pour les hommes. Près d'un sur cinq (19%) avait une consommation légèrement supérieure, et 10% une consommation nettement supérieure à ces limites. Par contre, 13% des participants ne buvaient pas d'alcool.

Les analyses ont examiné l'association entre la consommation d'alcool et les facteurs suivants, évalués entre 2004 et 2008: fragilité, vitesse et régularité de la marche, nombre de visites médicales et d'hospitalisations. Les résultats ont montré que les performances de marche (vitesse et régularité) étaient significativement moins bonnes chez les personnes rapportant une consommation d'alcool nettement supérieure aux recommandations. En revanche, les résultats n'ont pas permis de confirmer l'hypothèse qu'une consommation supérieure aux recommandations aurait un effet négatif sur la fragilité et sur la consommation de soins. Deux éléments peuvent expliquer ces résultats. D'abord, les personnes dont la santé est atteinte arrêtent souvent de boire de l'alcool. Par ailleurs, une consommation modérée peut avoir un effet bénéfique. Cette deuxième explication a été observée en particulier pour la fragilité : parmi les personnes initialement non-fragiles, les buveurs d'alcool avaient un risque moins élevé de devenir fragiles que les abstinents, y compris lorsqu'on tenait compte du fait que ces derniers avaient plus de maladies chroniques. En fait, une association négative a été observée entre l'abstinence et chacun des facteurs examinés, mais cet effet disparaissait lorsqu'on prenait en considération l'état de santé moins bon des personnes abstinentes (certaines ayant justement arrêté de boire pour des raisons de santé).

Ce travail met en évidence qu'un jeune senior sur trois rapporte une consommation d'alcool supérieure aux quantités recommandées pour la santé. Malgré le peu de conséquences négatives observées dans cette étude, ces résultats ne devraient pas servir à encourager la consommation d'alcool, notamment à cause d'autres risques comme les chutes et les accidents.

## SUMMARY

Several studies suggested a benefit of moderate drinking on cardiovascular disease and mortality, while no safe cut-off of alcohol use has been identified for cancer, hypertension or injury. The threshold between benefit and risk is of particular concern in older persons, who might be more vulnerable to relatively low levels of alcohol intake**.**

This work first describes the pattern of alcohol drinking in community-dwelling adults aged 65 to 70 years (N=1564), who participate into the Lausanne cohort 65+ study. Most participants (58%) were light-to-moderate drinkers (i.e. women: ≤1 drink/day, men: ≤2 drinks/day), while 29% drank above these recommended thresholds (19% were considered "at risk" and 10% "heavy" drinkers, this latter threshold defined as ≥2drinks/day (women), ≥3 drinks/day (men).

Then, using data collected from 2004 to 2008, analyses examined the association between these different levels of alcohol use and the following outcomes: prevalent and incident frailty; gait performance at baseline and follow-up; the use of health services (physician visits and hospital admissions). Contrary to our a priori hypotheses, few of these outcomes were negatively affected by drinking above recommended thresholds, and only gait performance was significantly poorer in heavy drinkers. The lack of significant association found with most other outcomes probably result from the combined impact of a healthy survivor effect and a beneficial effect of moderate alcohol consumption. This effect was more obvious in the analysis of the association with frailty: all subgroups of initially non-frail drinkers had a significantly lower risk of incident frailty than non-drinkers, even after adjusting for health status.

At the other end of the spectrum, abstinence was associated with poorer gait performance, a higher use of health services and a higher risk of frailty. However, these associations disappeared when adjusting for comorbidity, suggesting a confounding effect of underlying health problems in non-drinkers, the so called "sick-quitter" effect.

This work highlights that several methodological challenges are to take into account when designing studies that aim at investigating the effect of alcohol intake on older persons' health, mainly the sick quitter and healthy survivor effects. Despite its mostly negative findings, this work provides important information about alcohol consumption in the young-old population. A striking finding is that one in three young-old persons drinks above recommended levels, and is likely at risk of occasional heavy drinking, with accrued risk for

falls and accidents. These persons might feel too young to be concerned by recommendations targeting the older population. Messages targeting more specifically this young-old population might therefore be necessary to improve this result.

# 1 Introduction

## *1.1 Effects of alcohol consumption on health*

Alcohol use has been identified as a determinant of physical and mental health in adults. On the one hand, excessive alcohol drinking damages the hepatic and cardiovascular systems (1, 2). Alcohol abuse is also detrimental to cognition, both directly as a neurotoxic substance and indirectly through hypertensive effects (2). Most importantly, alcohol-related morbidity occurs at drinking levels below those typically associated with alcohol abuse or dependence. Regarding the risk of cancer, meta-analyses of recent studies showed a linear increase in the risk for most cancers even for low alcohol use (3, 4). As a consequence, no safe level of alcohol consumption has been highlighted regarding the risk of cancer. Similar observation have been made for a set of other problems such as hypertension, cirrhosis, hemorrhagic stroke, injuries and violence (5).

On the other hand, a rich literature describes potential benefits associated with moderate alcohol use. In particular, several studies suggest that moderate drinking decreases the risk of coronary heart disease, with a J-shape relationship between alcohol consumption and cardiovascular mortality (6-8). Similarly, a growing body of literature highlights possible benefits of moderate drinking on cognition, by preserving brain perfusion through preventing vascular damage (9, 10).

Although potential health benefits related to moderate alcohol use have been widely disseminated in both the scientific and laic literature, they remain subject to controversy. Studies of all-cause mortality provide even more conflicting results in support of the J-shaped curve, depending on study design and on the definition of the reference group. The protective

effect of alcohol has been claimed to be overestimated by including ex-drinkers in the reference group, in relation with the so-called *"sick quitter"* effect, i.e. drinkers quitting because of health problems (11-13). At the other end of the spectrum, an explanation to the increase in mortality risk among heavier drinkers might be attributable to different drinking patterns (episodic heavy drinking) or beverages (14). Additionally, a bias towards selective publication of studies showing an inverse relationship between moderate alcohol use and coronary heart disease has been observed by the authors of a meta-analysis (12) and probably also affects the literature focusing on alcohol and cognition or all-cause mortality. Nevertheless, a hierarchical meta-analysis by Gmel found a consistent beneficial effect of light to moderate alcohol use under all scenarios (15).

### *1.2 Effects of alcohol in older persons*

Most studies have been conducted among middle-aged men and women, and, although similar findings have been found in persons aged about 65 to 75 years, the threshold between benefits and risk is of particular concern in older persons, because age-related physiological changes and potential interaction with drugs make them more vulnerable to relatively low levels of alcohol (16, 17). Older women might be particularly at risk, as they have a lower lean body mass than men and more frequently use psychotropic medication (18-20). Alcohol intake usually declines with increasing age (21), but this decline seems attenuated in recent cohorts of older persons (22).

A study conducted among women aged 70-75 years at baseline and followed-up during 6 years observed that a low intake of alcohol (3-12 drinks per week) was associated to a lower mortality and a higher health-related quality of life, as compared to abstinence (23). Moderate drinkers also had better functional status, being less often impaired in their activities of daily

living (24-26). Regarding cognitive abilities, moderate drinking has been shown to lower the risk of developing dementia, an effect attributed to the protective effect of alcohol on vascular diseases (27-32). Nevertheless, alcohol use is also reported to be detrimental to brain cells, with brain shrinkage especially in the cerebellar area (32-34). These effects on brain are dose-dependent, but might develop with lower intake among older persons.

At a time when the number of older persons increases in most western population, these contrasting findings about specific risk-benefit ratio of alcohol consumption makes it especially timely and important to clarify recommendations regarding safe levels of consumption in old age.

### *1.3 Recommendations for a safe use of alcohol in older persons*

Interestingly, although lower levels of alcohol consumption are advocated in older persons, only a few countries issued specific recommendations targeting this population, and the cut-off level for a safe drinking varies across these countries. For instance, the U.S. National Institute on Alcohol Abuse and Alcoholism (NIAAA) recommends that people aged 65 years and older limit themselves to one drink per day (35). In Italy, guidelines advise older persons to consume no more than 30g in men and 25g in women, corresponding to 2 and 1,5 glasses of wine per day (www.sinu.it). In Switzerland, the Swiss Institute for Prevention of Alcoholism aims to make older persons aware of changing effects of alcohol with ageing, and to cut down their consumption accordingly. They might continue to drink up to 1 (women) or 2 drinks (men) per day in the absence of disease and if they subjectively judge their tolerance to alcohol as good (www.ispa.ch).

### *1.4 Justification of the work*

Although numerous studies in middle-aged persons observed a J-shape relationship between increasing alcohol consumption and cardiovascular disease with a beneficial effect of moderate alcohol use, it remains unclear whether the shape of this association remains similar in older adults. In particular, the cut-off between beneficial and detrimental intake of alcohol might vary with age, because older persons might be more susceptible to detrimental effects of lower levels of alcohol.

An additional question relates to some adverse outcomes that affect more specifically the older population but did not receive much attention in published literature. In particular, few studies investigated in this age group the impact of alcohol intake beyond recommended limits on the occurrence of frailty and on gait performance, as well as on the use of health services.

# 2 Aims of the study

First, this work intended to **describe the pattern of alcohol consumption** in the Lausanne cohort 65+ study, a large cohort of young-old persons.

More specifically, this study aimed to investigate the association of different levels of alcohol with **frailty** and **gait performance**. Using data from a prospective cohort study allowed examining these associations in longitudinal analyses. Prospective data were also used to examine the **use of health services** according to alcohol intake.

The present dissertation work is structured as follows: after a description of the methods, the first part of the results section presents the descriptive analyses about alcohol consumption in the study population **(Part 1, page 20)**. Then, the main results of three studies about the relation between alcohol use and **frailty (Part 2, page 22 and Annex 2)**, **gait (Part 3, page 24 and Annex 3)**, and **health services use (Part 4, page 27 and Annex 4)** are briefly summarized with the corresponding manuscripts enclosed. Finally, results of these different analyses are discussed altogether and put into perspective.

# 3 Methods (Article 1; Annex 1)

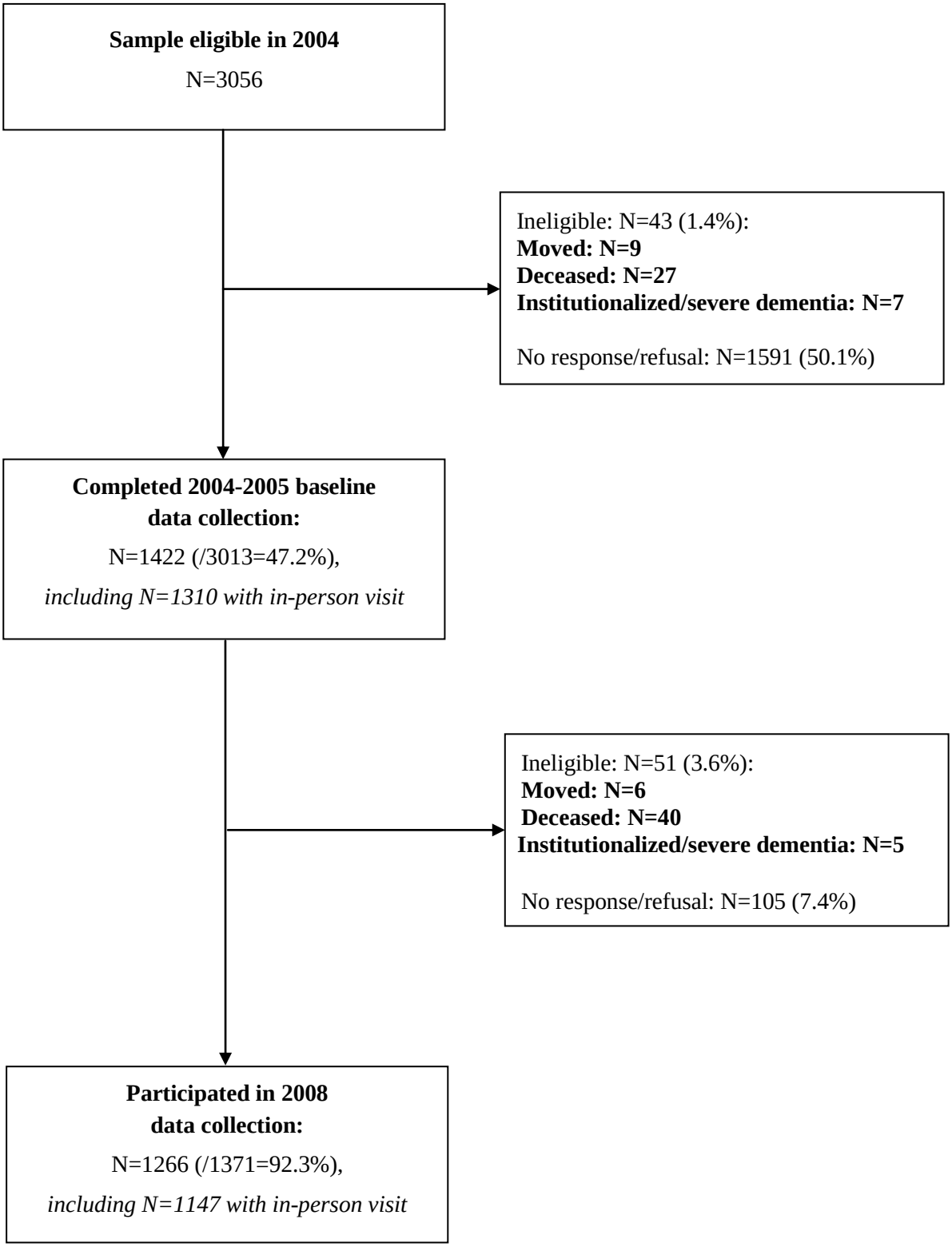
## *3.1 Study population and design*

In 2004-2005, the Lausanne cohort 65+ enrolled 1564 randomly selected community-dwelling persons aged 65 to 70 years. Data were collected using a self-completed questionnaire on socio-demographics and health, followed by a face-to-face interview with physical examination and performance tests.

Follow-up consisted of yearly self-completed questionnaires with additional in-person interview and physical assessment at 3-years intervals including the same physical and performance tests as performed at baseline. **Figure 1** shows the flow chart of participants over years 2004-2008. Deaths were ascertained on an annual basis using the local population register.

The Lausanne cohort 65+ protocol was approved by the Cantonal Human Research Ethical Committee (Commission cantonale d'éthique de la recherche sur l'être humain), and written consent was obtained from all participants during the in-person visit.

**Figure 1: Flow diagram of Lc65+ participants over the years 2004 to 2008**



### *3.2 Measurement of alcohol intake*

At baseline and 3-year follow-up, participants self-reported alcohol consumption over the past 12 months, using the AUDIT-C (36). The average number of standard drinks (wine, beer, spirits) consumed per week was determined using the first and second questions of the instrument. The answers to the question "How many drinks containing alcohol do you have on a typical day when you are drinking?" were modified to get more precise estimation about intake (1, 2, 3-4, 5-6, 7-9, 10+ drinks).The AUDIT-C also assesses the frequency of binge drinking, defined as 6+ drinks on one occasion.

In 2011, participants who kept on reporting no alcohol intake (N=70) were asked whether they never drank alcohol in their life or did stop drinking. Former drinkers were then asked about the timing and reasons for their decision.

#### 3.2.1 Operationalization of the alcohol variable

As detailed in **Table 1**, alcohol intake was categorized into "none", "light-to-moderate", and "excessive", based on published recommendations regarding safe alcohol consumption (35, 37, 38). "Light-to-moderate" drinking was defined as a maximum of 1 drink per day in women, ***without*** any binge drinking, and 2 drinks per day in men, ***with*** binge drinking tolerated less than once a month. "Excessive" drinking corresponded to any consumption beyond recommended thresholds, and was further classified into two sub-categories: "at risk" and "heavy". The threshold separating "at risk" from "heavy" drinking (Table 1) was defined based on cut-offs used in similar studies (≥12 drinks/week and/or binge drinking ≥1x/month for women, and ≥20 drinks/week and/or binge drinking ≥1x/week for men) (24, 26, 35).

The different study hypotheses were examined using this operationalized variable.

**Table 1 : Definition of drinking groups**

| **Drinking groups** | | **Alcohol intake** (drinks per week) | | **Frequency of binge drinking** (6+ drinks in one occasion) |
|---|---|---|---|---|
| **Not drinking** | | - | and | - |
| **Light-to-moderate** | Women | 1-7 | and | Never |
| **drinking** | Men | 1-14 | and | never or <once a month |
| **Excessive drinking :** | | | | |
| **At risk drinking** | Women | 1-7 | and | <once a month |
| | | or 8-11 | and | never or <once a month |
| | Men | 1-14 | and | once a month |
| | | or 15-19 | and | <once a week |
| **Heavy drinking** | Women | ≥ 12 | or | ≥ once a month |
| | Men | ≥ 20 | or | ≥ once a week |

### *3.3 Measurement of outcomes*

Outcomes examined in this work were assessed at baseline and 3-year follow-up, except for the use of health services which was reported at baseline and at each annual follow-up from 2005 to 2008.

#### 3.3.1 Measurement of frailty

Frailty was measured using Fried's frailty phenotype, which is based upon impairment in five domains: nutrition, endurance, physical activity, muscle strength, and slowness (39). Frailty criteria were operationalized as follows:

- ***Nutritional problem*** was defined as any self-reported involuntary weight loss in prior year.
- ***Poor endurance*** was assessed through self-reported significant fatigue and/or lack of energy in the last four weeks.

- ***Low physical activity*** corresponded to self-reporting all of <20 minutes of sports per week, <90 minutes walking per week, and avoiding climbing stairs or carrying light loads in daily activities.
- ***Low muscle strength*** was measured through low grip strength (best out of three measurements), using the sex-and body-mass specific cut-off values of the original frailty definition in the Cardiovascular Health Study.
- ***Slowness*** was measured through walking over 20 meters at usual self-selected speed, using the sex-and height specific cut-off values of the original frailty definition in the Cardiovascular Health Study.

Frailty was defined according to Fried's classification: individuals meeting one or two criteria were considered as pre-frail, and those with three or more criteria as frail. Regarding the low prevalence of frailty in the study's age range, frail (2.3%) and pre-frail (26.1%) participants were merged into a single "**vulnerable**" category (presence of ≥1 Fried's criteria), all other participants being considered as "**robust**" (0 criterion).

### 3.3.2 Measurement of gait parameters

Gait parameters were recorded while walking over 20 meters at self-selected, usual speed in a well-lit walkway, during single and dual task. During dual task, participants were asked to count backwards aloud from fifty while walking. Gait speed (m/s) was estimated from the angular velocity recorded by body-fixed sensors using the Physilog® system (BioAGM, Tour-de-Peilz, Switzerland (40)). Gait speed variability was assessed with the coefficient of variation (CV in %) defined as the standard deviation divided by the mean value of gait speed for each stride.

### 3.3.3 Measurement of health services use

Each year, participants reported how often they visited a physician over the previous 12 months, and whether they were hospitalized, allowing to estimate the cumulative number of physician visits and hospital admissions over 5 years. They also had to indicate how many of these visits and hospital admissions were unplanned.

## *3.4 Statistical analyses*

Descriptive statistics examined the frequency and amount of alcohol intake in this population. To describe participants' characteristics associated with different levels of alcohol intake, bivariate associations between categories of alcohol intake and health variables were examined using the chi-squared test and analysis of variance for categorical and continuous variables, respectively (Part 1).

Then, unadjusted regression models examined the association between categories of alcohol intake and the different outcomes of interest. Logistic models were used for binary outcomes (Part 2: frailty), while robust linear regression analyses were performed for continuous ones (Part 3: gait speed and gait variability). Robust regression was selected to account for heteroscedasticity, i.e heterogeneity of the variance distribution. Finally, negative binomial regression models were used for count variables (Part 4: number of physician visits/number of hospital admissions) whose variance exceeded the mean.

Multivariable analyses were then performed to examine the relation between alcohol use and the different outcomes under study (Part 2 to 4), using the "light-to-moderate" drinkers as reference group. Potential confounders selected as adjustment variables were: education, chronic conditions, cognitive impairment, functional status. Other adjustment variables were added according to the outcome under study.

As men and women displayed different patterns of alcohol consumption, significance of a gender-alcohol interaction was tested for each outcome and showed up to be not significant.

In order to investigate the prospective association between baseline alcohol intake and outcomes under study over the 2005-2008 period, the following analyses were performed:

1) Incident vulnerability (Part 2): the analysis was restricted to participants who were robust at baseline, and further adjusted for significant changes in alcohol consumption between 2005 and 2008.
2) Decline in gait performance (Part 3): logistic models examined whether the proportion of participants who declined in gait speed, or respectively, increased their gait speed variability, varied according to baseline alcohol intake, during usual and dual task walking. Regarding gait speed, based on previous works, the outcome was a decline of 0.1m/s, considered as a clinically meaningful change (41).
3) Use of health services (Part 4): binomial regression models investigated the association between the level of alcohol use and the 5-year mean cumulative number of physician visits and hospital admissions, respectively.

All analyses were conducted using Stata, version 13.0.

# 4 Part 1: Description of alcohol use

At baseline, complete data on alcohol-related variables were available for 1437 of the 1564 (91.9%) participants. Overall, 92.9% of men and 83.4% of women did report some consumption of alcohol over the previous 12 months. **Table 2** shows baseline characteristics of participants, as well as their comparison across the four drinking categories. Only 13% of the participants did not drink alcohol, 57.8% were light-to-moderate drinkers, and 29.2% were excessive drinkers (18.7% "at risk" and 10.5% "heavy"). Comparisons across the four drinking groups showed increasing proportions of men, as well as of current smokers as alcohol intake increased. Non-drinkers displayed the highest proportion of poor self-rated health, comorbidity, functional impairment, and previous alcohol-related problems. A similar pattern, although less pronounced, was observed in heavy drinkers. Cognitive impairment was rare altogether (2.8%), but significantly more frequent in non-drinkers.

During follow-up, alcohol consumption remained quite stable in non-drinkers and moderate drinkers. For example, between 2005 and 2008, 75% of non-drinkers and 85% of light-to-moderate drinkers remained in the same group. In contrast, about 40% of excessive drinkers decreased their alcohol consumption and were classified in a lower category of alcohol intake in 2008.

Data collected in 2011 in the subsample of non-drinkers (N=70) indicated that most of them were past drinkers (n=43), who in many cases quitted because of health (n=18) or alcohol-related problems (n=10).

**Table 2: Characteristics of the population and comparison between drinking groups**

| | Drinking groups | | | | | |
|---|---|---|---|---|---|---|
| | Total | Not drinking | Light-to-moderate | At risk | Heavy | P-value* |
| | N=1437<br>100% | N=187<br>13.0% | N=830<br>57.8% | N=269<br>18.7% | N=151<br>10.5% | |
| Age (mean ± SD) | 67.0±1.4 | 67.1±1.4 | 67.1±1.4 | 66.8±1.4 | 66.9±1.4 | .156 |
| Men (%) | 42.7 | 24.1 | 40.8 | 51.7 | 59.6 | <.001 |
| Low education (%) † | 65.5 | 71.9 | 63.3 | 66.7 | 68.0 | .126 |
| Current smoking (%) | 21.1 | 16.8 | 18.1 | 24.5 | 36.7 | <.001 |
| Poor self-rated health (%) | 34.8 | 47.1 | 34.2 | 25.8 | 39.1 | <.001 |
| Comorbidity ($2^+$ diseases, %)‡ | 49.1 | 62.4 | 47.5 | 48.1 | 44.0 | .001 |
| Cognitive impairment (%) § | 2.8 | 7.0 | 2.1 | 2.9 | 1.7 | .015 |
| Instrumental ADL impairment (%)‖ | 15.5 | 28.3 | 13.7 | 13.7 | 14.1 | <.001 |
| Basic ADL impairment (%)¶ | 10.8 | 19.4 | 9.5 | 7.8 | 14.1 | .001 |
| Previous alcohol-related problem (%) | 4.6 | 13.9 | 1.7 | 4.5 | 9.9 | <.001 |

* P-value from Chi-square test (categorical variables) or ANOVA (continuous variables)
† Defined as less than 12 years of education (compulsory school or apprenticeship)
‡ Defined as self-reporting 2 or more out of 12 common medical diagnoses
§ Defined as a score <24/30 at Folstein's Mini-Mental State Examination [14]
‖ Defined as any difficulty/need for help in Instrumental Activities of Daily Living (shopping, and performing usual household activities) [12]
¶ Defined as any difficulty/need for help in Basic Activities of Daily Living (include bathing, dressing, using the toilet, transferring into/out of bed or chair, feeding) [11]

# 5 Part 2: Alcohol and frailty (Article 2; Annex 2)

## *5.1 Background*

Age-related frailty is a condition of increased vulnerability that conveys a high risk for morbidity, disability, and mortality (39). Using Fried's frailty phenotype, both frail and pre-frail individuals have been shown to experience more frequent adverse outcomes and thus can be considered as vulnerable.

In view of the existing relationship between alcohol use and multiple health outcomes, in particular mortality, one can hypothesize that a similar relation might exist between alcohol consumption and frailty. Although there is a large and growing body of literature about frailty, very few studies to date specifically examined the association between alcohol and frailty. Overall, these studies showed that moderate alcohol intake was associated both in cross-sectional and longitudinal analyses with a lower risk of frailty (42-44).

## *5.2 Aim and hypotheses*

Given the paucity of data, we aimed to investigate the independent association between alcohol consumption and frailty, as measured by Fried's phenotype, both cross-sectionally and prospectively. For the purpose of the present work, frail (2.3%) and pre-frail (26.1%) participants were merged into a single "vulnerable" category (presence of ≥1 Fried's criteria), all other participants being considered as "robust" (0 criterion).

Study hypotheses were that older persons who do not currently drink alcohol and those with alcohol intake above recommended threshold (i.e., "At risk" and "Heavy" drinking groups) will both be more likely to be vulnerable (prevalent vulnerability) as well as to become vulnerable (incident vulnerability) over time.

### *5.3 Results*

At baseline, vulnerability was most frequent in non-drinkers (43.0%), least frequent in light-to-moderate drinkers (26.2%) and "at risk" drinkers (23.5%), and amounted to 31.9% in "heavy" drinkers, thus showing a reverse J-curve pattern. This pattern was more pronounced in women than in men. In multivariate analysis adjusting for health, functional status, and baseline alcohol consumption, non-drinkers remained at twice higher odds of prevalent vulnerability (adjOR: 2.24; 95%CI: 1.39 to 3.59; p=.001) compared to light-to-moderate drinkers. Heavy drinkers also were slightly but not significantly at higher odds of being vulnerable (adjOR: 1.39; 95%CI: 0.86 to 2.25; p=.173).

During the three-year follow-up period, the proportion of robust participants at baseline who transitioned toward vulnerability was highest among those who did not drink at baseline. Results from multivariate analysis showed that non-drinkers had twice higher odds than light-to-moderate drinkers of incident vulnerability (adjOR: 2.00; 95%CI: 1.02 to 3.91; p=.043). In contrast, no significant association was observed among "at risk" and "heavy" drinkers.

### *5.4 Discussion*

Although residual confounding is still possible, these results likely reflect a healthy survival effect among drinkers. They probably result from both a "sick quitter" bias (i.e., individuals who experienced health- or alcohol-related problems stop drinking), and a beneficial effect of alcohol. An additional important finding was that almost 30% of these young-old persons drank more than recommended, and had a non-significantly increased risk of vulnerability.

# 6 Part 3: Alcohol and gait performance (Article 3; Annex 3)

## *6.1 Background*

The consequences of chronic alcohol abuse on gait and balance are well known (2, 16, 17), but possible effects of a moderate consumption on gait parameters still received little attention. Some studies observed that even moderate alcohol use might over the long term affect cerebellar cells, causing ataxia and higher body sway, but the impact on gait performance, in particular gait velocity and variability, remains controversial (34, 45, 46).

Alcohol effects may not be obvious during usual walking, but might become more evident when simultaneously performing a cognitive task, such as counting backwards. Gait has been shown to slow and variability to increase, especially when cognitive performance is altered, showing the inability to allocate attention properly between counting and walking (47-49). As alcohol also causes cortical brain damage, dual tasking might help to reveal negative consequences of alcohol use in subjects who drink beyond recommended threshold. However, the protective effect of moderate alcohol use against vascular diseases (6, 7) might counterbalance the potential detrimental influence of alcohol on gait, by preventing damage to cerebral circulation.

## *6.2 Aim and hypotheses*

This analysis aimed to investigate the association between different levels of alcohol use and gait performance at baseline and three-year follow-up.

We hypothesized that higher alcohol consumption would be associated with slower gait speed and higher gait speed variability at baseline, and with greater decline in gait performance (i.e.

slower gait speed and/or increased variability) at follow-up. In addition, the negative influence of higher alcohol intake on gait was expected to be more evident under cognitive dual-task condition.

### *6.3 Results*

Overall, gait speed was 1.13±0.16 m/s under single task and decreased to 0.99±0.19 m/s in dual task (counting backwards). Average gait speed variability in the entire sample was 3.5% under single task condition, and increased to 6.2% during dual task.

Compared to light-to-moderate drinking, heavy drinking was associated with slower gait speed in single task (adj. coeff: -.043, 95%CI: -.0.80 to -.005, p=.025), and dual task, although this latter effect was not significant. No significant association was observed between heavy drinking and gait speed variability. Non-drinkers walked slower and with higher speed variability than light-to-moderate drinkers, both in single and dual tasks, but these associations did not remain significant after adjustment for comorbidity.

At 3-year follow-up, 35.2% and 34.1% of the participants walked significantly slower in single and dual-task, respectively. This proportion varied only marginally across drinking categories. However, more participants were lost to follow-up gait measurement in the non-drinking and heavy drinking groups (>20% of the baseline sample) as compared to the light.-to-moderate and at risk groups (<15% of the sample), notably because they could not perform walking test. Participants lost to follow-up gait measurement had significantly slower gait speed and increased gait variability at baseline as compared to those followed-up.

### *6.4 Discussion*

At baseline, heavy alcohol consumption was significantly associated with slower gait speed in single task. Selective attrition and healthy survival effect probably explain why the

association was not retrieved in longitudinal analyses. The observation that participants lost to follow-up had worse gait performance at baseline, as well as the increased death rate among heavy drinkers support the hypothesis of a healthy survivor effect. This likely resulted in underestimation of the deleterious effect of heavy alcohol intake on gait performance at follow-up. The observed trend of poorer gait performance in non-drinkers disappeared after adjustment for comorbidity, suggesting confounding by a poorer health status.

# 7 Part 4: Alcohol and health services use (Article 4; Annex 4)

## *7.1 Background*

Alcohol use may impact on health services utilization because of consequences of acute intoxication, such as accidents, as well as secondary to health problems enhanced by chronic excessive drinking (cirrhosis, stroke, depression,…). The nature of this association has been shown to be inconsistent among middle-aged and older adults (50-54), probably because of different study designs and outcomes (inpatient vs outpatient/planned vs unplanned services).

A U-shaped association has been reported with the use of inpatient services, especially in the emergency department: life-long abstainers, past drinkers and heavy drinkers are more frequent users than low drinkers (50). Interestingly, adults with alcohol consumption just above recommended levels were also shown to have higher risk of alcohol-related hospital admission (53). In contrast, the association with outpatient care use seems reverse in these persons (50, 55). This is particularly noticeable for preventive care, partly because low drinkers appear to have more health-conscious behaviors (56). The higher use of planned services by non-drinkers might be explained by the fact that some of them abstained because of chronic conditions since childhood.

## *7.2 Aim and hypothesis*

Given the scarcity of information on this topic, this work examined the association between alcohol intake and the number of physician visits, as well as of hospital admissions over 5 years. Study hypotheses were that alcohol use above recommended cut-offs would be associated with a higher number of hospital admissions, and a higher number of unplanned physician visits, but with a lower number of planned visits.

### *7.3 Results*

Overall, the mean cumulative number of planned physician visits over five years was 27.8. There was a clear inverse relationship with alcohol consumption, as visits decreased from 34.0 in non-drinkers to 27.6, 25.9 and 25.0 in light-to-moderate, at-risk and heavy drinkers, respectively (p=.02). Regarding unplanned visits, their mean cumulative number was 3.0, without significant difference across categories of alcohol drinking.

Almost half of the participants did report at least one hospitalization during the previous five years, with a mean of 2.2 admissions among users. The proportion of persons with at least one hospital admission was slightly, although not significantly, lower among heavy drinkers as compared to the other groups. However, the mean cumulative number of hospital admissions did not vary according to alcohol intake. In multivariate analyses that adjusted for socio-demographic and health variables, alcohol intake was not significantly related to the use of either physician visits or hospital admissions as an independent factor. Comorbidity and poor self-rated health were significant determinants of each outcome.

### *7.4 Discussion*

Contrary to our hypotheses, this analysis did not demonstrate any positive association between higher intake of alcohol and the use of health services. On the contrary, the number of planned physician visits showed a non-significant decrease from low to heavy drinkers. Several explanations are likely to explain these findings, including the sick quitter (in nondrinkers) and healthy survivor (in heavy drinkers) effects. Notably, the higher use of physician services in non-drinkers disappeared once adjusting for comorbidity, suggesting confounding by a poorer health profile, further supporting the sick quitter hypothesis. Finally, low-to-moderate drinkers had higher use of planned physician visits as compared to other drinkers, a finding likely attributable to more health conscious behavior.

# 8 Synthesis

This work aimed to describe the pattern of alcohol drinking in a large sample of community-dwelling older adults, and to investigate the association between different levels of alcohol intake and frailty, gait performance, and the use of health services, outcomes of importance that have been scarcely studied in the older population. Several observations from the current study contribute to the rare data on the association between alcohol use and these health-related outcomes.

## *8.1 A high prevalence of alcohol use*

This group of persons aged between 65 and 70 years reported a high consumption of alcohol. Switzerland is a country with high intake of alcohol related to cultural determinants. In particular, the Western part of Switzerland, where this study was conducted, has a strong history of wine production and it was expected that only a minority of participants would be abstainers. Indeed, only one in ten reported no alcohol intake over the past twelve months, but one in three drinkers over passed thresholds recommended in this age group. These results are consistent with those of another study that enrolled participants in the same city (57).

## *8.2 Limited effect of alcohol intake beyond recommended limits on studied outcomes*

Most results showed a trend supporting the hypothesis of a deleterious effect of alcohol intake beyond recommended limits on the outcomes under study (Table 3). However, the only significant association observed was decreased gait speed in heavy alcohol users. Some potential methodological explanations for this lack of significant results are proposed thereafter. In addition, this difficulty to highlight harmful effects of high alcohol intake on older persons' health might also participate to the paucity of published literature on this topic, as negative studies are less likely to get published.

At the other end of the spectrum, abstinence was associated with a higher probability of prevalent vulnerability, poorer gait performance, and higher health services use in cross-sectional analyses. In addition, abstinence was also associated with twice higher odds of transition toward vulnerability during the 3-year follow-up period. Yet, the sensitivity of these results to adjustment for comorbidity strongly suggests a confounding effect of underlying health problems in these older persons.

**Table 3: Synopsis of the results from multivariate analyses of the association between alcohol use and outcomes under study**

| | | Expected direction of the association with at risk/heavy drinking | Level of alcohol drinking | | | |
|---|---|---|---|---|---|---|
| | | | No drinking | Light-to-moderate | At risk | Heavy |
| Frailty | Prevalence | + | + | ***reference group*** | - *ns* | + *ns* |
| | Incidence | + | + | | + *ns* | - *ns* |
| Gait speed | Single task | - | - *ns* | | - *ns* | - |
| | Dual task | - | - *ns* | | + *ns* | - *ns* |
| Gait variability | Single task | + | + *ns* | | - *ns* | - *ns* |
| | Dual task | + | + *ns* | | + | + *ns* |
| Nb physician visits | Planned | - | + *ns* | | - *ns* | - *ns* |
| | Unplanned | + | + *ns* | | - *ns* | + *ns* |

**Interpretation of the symbols: +** indicates a positive association, **-** indicates a negative association, *ns* means that the association is not statistically significant after adjustment. Grey cells indicate statistically significant results ($p<.05$).

Overall, these findings probably result from the combined impact of:

- **A beneficial effect of moderate alcohol use**: this benefit was mostly observed for analyses related to frailty, a result in line with the only two studies that investigated this association previously (42, 43). All subgroups of drinkers had lower risk of incident frailty than non-drinkers, even after adjusting for health status. As cardiovascular diseases are most prevalent in older persons and heavily contribute to the frailty process, this finding

could be explained by a reduction in cardiovascular morbidity resulting from moderate alcohol use.

- **The "sick-quitter" effect** (15): information about life-long alcohol use was available in 2011 for the subsample of participants who did not report drinking any alcohol over the previous twelve months: half of them were ex-drinkers, most of whom stopped because of general health or specific alcohol-related problems. Interestingly, never drinkers and ex-drinkers were quite similar in terms of comorbidity, poor self-rated health, and baseline vulnerability status, but the former more frequently reported noteworthy health problems during childhood. Thus, in a country with a high prevalence of alcohol drinking, never drinkers seem to be a selected sample of persons who clearly differ from the rest of the population in terms of health status.

  The sick quitter effect also potentially explains why chronic conditions were not more prevalent in heavy drinkers than in other drinkers, even for conditions typically associated with alcohol use like peptic ulcer or depression. Those conditions were most prevalent in non-drinkers.

- **The "healthy survivor" effect**: death ascertainment during a 6-year follow-up revealed that death rate was highest among heavy drinkers (15% vs 7% among light-to-moderate drinkers). This result suggests that, among heavy drinkers, the fittest individuals remained alive and kept on drinking.

A detrimental effect of drinking was found in relation with gait performance. Gait speed was actually slowest in heavy drinkers, potentially linked to the toxicity of alcohol on brain and

nerves, causing in particular polyneuropathy. Unfortunately, this information was not available and precluded further analyses to investigate this possible causal pathway.

### *8.3 An increased risk of acute adverse events among heavy alcohol users*

Although the risk of experiencing the adverse outcomes under study was not higher in heavy drinkers, excessive drinking is correlated with increased occurrence of binge drinking, which conveys a risk for accidental injuries. Notably, we observed that the proportion of recurrent fallers, as well as the proportion of participants reporting any accidental injury, was highest among heavy drinkers in comparison to at risk and moderate drinkers. These outcomes were not the focus of this research. Nevertheless, these findings indicate an increased risk of acute adverse events in heavy drinkers.

### *8.4 Strengths and limitations of the study*

#### 8.4.1 Representativeness

This work relies on a large sample of community-dwelling older adults representative of the general population of the same age in the city of Lausanne. The lower likelihood of enrolling heavy drinkers in studies about health might result in an underestimation of the true prevalence of problem drinking, but this is probably inherent to every population-based study. For instance, consumption patterns observed in the current study were very similar to those observed in the Swiss Health Survey and in the COLAUS study (57), that both displayed a similar proportion of heavy drinkers. A larger sample of heavy drinkers would have increased the statistical power in several analyses (e.g., gait variability) and allowed some further analyses.

### 8.4.2 Validity of alcohol measurement

Social desirability bias, i.e. underreporting the quantity of alcohol intake, is present whenever alcohol use is self-reported. To minimize this bias, participants reported alcohol use on a self-completed questionnaire, not during face-to-face interview. The use of the AUDIT-C has the merit of relying on a validated questionnaire. Although the possible answers do not provide a precise quantity of alcohol, precluding to use this information as a continuous variable, they allow to determine the amount of alcohol intake with sufficient accuracy to define the categories used in this work, based on potential risk.

### 8.4.3 Validity of outcomes measurement

Frailty was assessed using its most widely used definition, Fried's frailty phenotype, which has been shown to predict a range of adverse outcomes, such as falls, hospitalization, disability, and death (39, 42, 58). A criticism towards this definition is that it mostly encompasses physical components. Although depressive problems are likely captured through the "exhaustion" criterion (59), Fried's frailty phenotype overlooks cognitive problems, which likely contribute to the pathway from robustness to frailty.

Gait performance was assessed using the Physilog® device. This device has been shown to be able to detect subtle changes in gait speed and variability, with suitable accuracy when compared the gold standard of videorecording and monitoring (40). Given the detrimental effect of alcohol on balance through neurological damage, it might have been interesting to examine the association between alcohol intake and increased stride width. Unfortunately, the version of the Physilog used in the current study did not allow recording this parameter. It is to note that gait speed is also one frailty criterion, but the cut-off defining slow gait in Fried's

phenotype is really low, and was found in around 3% of Lc65+ participants. This likely explains why results for frailty and for gait were not comparable.

Finally, the number of physician visits and hospital admissions were self-reported. Previous studies showed poor concordance between self-reported use of health services and claims data, but there is no reason to suppose that such inconsistency would be distributed heterogeneously across categories of drinkers.

## *8.5 Recommendations for future studies*

This work highlights a number of methodological challenges to take into account when designing and interpreting studies that aim at investigating the effect of alcohol intake on older persons' health. Altogether, results point to the fact that it is difficult to demonstrate the detrimental effect of alcohol use in persons who are older than 65 years, mainly because of the combined sick quitter and healthy survivor effects. Participants may have stopped or reduced their alcohol intake before the start of the study or during follow-up. Therefore, studies should start examining this association in middle-aged adults and follow them until old age.

## *8.6 Implications and perspectives*

### 8.6.1 Implications for the population of older persons

One in three persons aged 65 to 70 years drinks above recommended levels. Even though this work did not show significant negative effects of this consumption on the outcomes under study, these results do not mean that older persons should be encouraged to drink. Rather, the overall risk associated with drinking may well outweigh any potential benefit for many older persons. Indeed, persons who drink more than recommended amounts are more likely to engage in occasional heavier drinking, with an increased risk for acute adverse events such as

falls and accidents. This population should be better informed about the specific risks of alcohol intake in ageing, as young old persons might not feel concerned by recommendations developed for the older population. Specific information campaigns specifically targeting the young old population have to be added to the existing interventions and policies aiming to reduce alcohol-related harm.

### 8.6.2 Implications for health professionals

Given the high prevalence of at risk drinking in young old persons, health professionals should periodically question their ageing patients on their alcohol-related habits and be able to provide counselling to reduce alcohol misuse. Despite a relatively small number of studies including older adults in primary care settings, data regarding the effectiveness of screening for alcohol misuse and of behavioural counselling conclude to a moderate benefit with low related harm (60, 61). This study also highlights that quitting alcohol might indicate worsening health, a result suggesting that health professionals should enquire about health problems in patients who change their drinking habits. Pharmacists could also play a role in informing and counselling when they identify older persons whose medication might confer a risk with alcohol use (62).

### 8.6.3 Implications for health policy

Alcohol is still very affordable in Switzerland, a country with a long tradition of wine making. Several studies documented that higher taxes on alcoholic beverages might reduce the level of consumption, but these studies mostly focused on younger population who have been shown more responsive to price changes than older persons (63, 64). In addition, as shown by another report on our sample, risky alcohol use was less frequent in participants who had a lower socio-economic status or financial difficulties, a finding also observed in other

European countries (65, 66). Further evidence is therefore needed regarding the effects of alcohol taxation on older population's behaviour. Other ways to address unhealthy drinking, for example by promoting alcohol-free social events, should also be considered in health policies.

### *8.7 Conclusion*

Alcohol consumption carries many hazards, while benefits through cardiovascular protection might be reduced in older persons. A substantial proportion of the young-old population reports drinking above the limits recommended for health and is likely to engage in occasional heavier drinking with immediate related risks. The lack of significant harmful effect of drinking on the outcomes in this study should therefore not be interpreted as the absence of alcohol-related health risk. Indeed, older persons who develop health problems tend to reduce their consumption. Interventions should aim to reduce alcohol use in at risk drinkers before the occurrence of such problems. Evidence on the effectiveness of measures aiming at reducing alcohol intake in older persons is limited, and further research should specifically target this population.

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# 10 Annex 1

Santos-Eggimann B, Karmaniola A, Seematter-Bagnoud L, Spagnoli J, Bula C, Cornuz J, et al. The Lausanne cohort Lc65+: a population-based prospective study of the manifestations, determinants and outcomes of frailty. BMC Geriatr. 2008;8:20.

BMC Geriatrics

Study protocol

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# The Lausanne cohort Lc65+: a population-based prospective study of the manifestations, determinants and outcomes of frailty

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## Abstract

**Background:** Frailty is a relatively new geriatric concept referring to an increased vulnerability to stressors. Various definitions have been proposed, as well as a range of multidimensional instruments for its measurement. More recently, a frailty phenotype that predicts a range of adverse outcomes has been described. Understanding frailty is a particular challenge both from a clinical and a public health perspective because it may be a reversible precursor of functional dependence. The Lausanne cohort Lc65+ is a longitudinal study specifically designed to investigate the manifestations of frailty from its first signs in the youngest old, identify medical and psychosocial determinants, and describe its evolution and related outcomes.

**Methods/Design:** The Lc65+ cohort was launched in 2004 with the random selection of 3054 eligible individuals aged 65 to 70 (birth year 1934–1938) in the non-institutionalized population of Lausanne (Switzerland). The baseline data collection was completed among 1422 participants in 2004–2005 through questionnaires, examination and performance tests. It comprised a wide range of medical and psychosocial dimensions, including a life course history of adverse events. Outcomes measures comprise subjective health, limitations in activities of daily living, mobility impairments, development of medical conditions or chronic health problems, falls, institutionalization, health services utilization, and death. Two additional random samples of 65–70 years old subjects will be surveyed in 2009 (birth year 1939–1943) and in 2014 (birth year 1944–1948).

**Discussion:** The Lc65+ study focuses on the sequence "*Determinants → Components → Consequences*" of frailty. It currently provides information on health in the youngest old and will allow comparisons to be made between the profiles of aging individuals born before, during and at the end of the Second World War.

## Background

Health and social security systems of industrialized countries are confronted with aging populations and must solve problems related to functional dependence over a wide scale resulting from an epidemic of chronic diseases. This unprecedented situation has prompted researchers to focus their efforts on studying relationships between chronic diseases and the development of disability [1,2], and documenting and forecasting related needs for chronic care. Functional dependency, however, mostly concerns the oldest old population, while demographic trends and population health over the next 30 years will be determined not only by the evolution of longevity, but also by the aging of the large cohort generated by the post-World War II baby-boom. Health and health care needs of this youngest old population have been less well studied. Baby-boomers will be affected by the consequences of cumulated chronic diseases in two decades from now, and preventing disability in this cohort should be considered a public health priority.

A logical approach is to study aging individuals not yet affected by disability. The concept of frailty [3,4] is of particular interest in this regard. A better understanding of the pathway leading from health to frailty and to disability is necessary for preventive intervention. Despite a large volume of recent publications on the subject, and a variety of models, definitions and criteria [5], frailty is still an evolving concept [3,6-8]. There is nevertheless a consensus view that considers frailty as a multidimensional geriatric syndrome with biological, physiological and psychosocial components, and as a state of increasing vulnerability and loss of adaptability to stress [5,9]. Rather than a dichotomous characteristic separating older subjects into two distinct subgroups, it is viewed as a progressive loss of capacity to adapt to complexity and to environmental stressors [10], and as a decline in the ability of an individual to withstand illness without loss of function (functional homeostasis) [11,12]. Campbell and Buchner [13] described frailty as a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure.

The detection and quantification of frailty in epidemiological studies necessitate some operational definition of this concept. The frailty model proposed by Fried et al. is one of the most frequently used and seems of particular interest for research since it integrates a description of a measurable frailty phenotype within a theoretical concept of causation, manifestations and consequences [14,15]. In this model, the clinical syndrome of frailty is influenced by diseases and by declines in physiologic function and reserve, and it results in adverse outcomes that range from falls to death. The Fried et al. phenotype relies on five items: unintentional weight loss or sarcopenia, weakness as measured by grip strength, poor endurance resulting in self-reported exhaustion, slowness as measured by walking speed, and self-reported low physical activity. It was developed in the context of the longitudinal Cardiovascular Health Study and validated in the Women's Health and Aging Studies [16]. At this stage of knowledge, the phenotype described by Fried et al. seems the most concrete as well as the most agreed upon way to detect frailty. Its frequency has been estimated in a few studies [16-21]. However, despite a consensus on its pertinence, several concerns about this phenotype could be raised. First, this phenotype likely neglects some important dimensions of frailty, as it contains mostly physical characteristics, even though the inclusion of self-reported exhaustion, which is frequently associated with depression, already indicates a contribution of mental health to the frailty syndrome [22]. The Fried phenotype will probably evolve to include additional dimensions such as cognitive and psychological characteristics. Second, the clinical applicability of this phenotype has been questioned and simplified versions need to be developed [23]. Third, there is much debate on the role of psychosocial and economic characteristics in the frailty syndrome. Key components of several multidimensional models of frailty, such as economic vulnerability, may act as determinants, as enhancers, or as outcomes of frailty. Finally, despite a growing body of literature, the chronology and temporal relationships between the different determinants of frailty remain largely speculative.

Improving our knowledge of frailty is particularly appealing because frailty may expose individuals to an increased risk of a range of adverse outcomes and constitute a reversible precursor of functional loss in old age [24,25]. Falls, injuries, acute illnesses, repeated use of emergency services, hospitalizations, disability, and death have been found to be associated with sub-clinical diseases and frailty [15,26-31]. As a result, frailty also appears to be a powerful indicator of health status and of health care needs of aging populations. From a public health perspective, the early detection and prevention of frailty may influence the progression of disability in aging populations [32]. This, however, requires improvements in our understanding of the "Determinants → Components → Consequences" sequence that characterizes age-related frailty.

### *Rationale and aims of the Lc65+ study*

The rationale for undertaking the Lc65+ study is the paucity of longitudinal epidemiological data specifically collected to improve our understanding of frailty as 1) a phenomenon resulting from various psychosocial and medical influences, 2) a manifestation of abnormal

decline in old age, and 3) a cause of evolution towards adverse outcomes, particularly functional decline and a high level of health services utilization. The ultimate goal of the Lc65+ study is to open the field toward developing and testing interventions to potentially reverse the frailty pathway. This study will provide essential information to shape individual and community-based preventive interventions, taking into account the opinions of frail older individuals and their caring environment, and recognizing the evolution of health and expectations across population groups born before, during and after the Second World War.

The specific aims of the Lc65+ cohort are to investigate:

a) the sequence of the physical and mental health manifestations of frailty ***(phenotype)***;

b) the relationship between subjective health and objective manifestations of frailty ***(perception)***; the extent to which frail individuals perceive their entry and progressions in the spiral of frailty is an essential question in public health, particularly for the quantification of frailty as a major indicator of health in aging populations, since survey data often rely essentially on self-reported data.

c) the trajectories and transitions between levels of frailty ***(natural history)***;

d) the environmental, medical and psychosocial determinants or other predictive factors for frailty ***(risk factors)***;

e) the effect of frailty on the risk of falls, functional impairments or dependency, secondary morbidity, health services utilization and death ***(impact)***;

f) the self-perceived and objective levels of health and frailty from the age of 65 years in individuals born before, during and after the Second World War ***(public health)***.

## Methods/design

### *Design*

The Lausanne cohort Lc65+ is a longitudinal, observational study initiated and conducted by the Institute of Social and Preventive Medicine at the University of Lausanne Hospital Center (Switzerland), in collaboration with clinical partners from the University of Lausanne Hospital Center (CHUV) and Department of Community Medicine and Health. The study protocol was approved by the Ethics Committee of the Faculty of Biology and Medicine, University of Lausanne. Three successive representative samples of the general community-dwelling population of about 1500 individuals each will be followed from age 65 to death (Figure 1). Subjects are enrolled at the age of 65 to 70 and give written consent for their participation.

### *Sampling and recruitment in 2004*

The first stage of sampling and recruitment in the Lc65+ study took place in 2004 (Figure 2). A similar procedure will be repeated in 2009 and 2014. Eligibility is defined by the place of residence (Lausanne, a Swiss city of 125000 inhabitants) and by the year of birth. Subjects living in an institution or unable to respond by themselves due to advanced dementia are excluded.

In April 2003, the Population Office extracted a list of city residents comprising 4879 individuals born between 1934 and 1938. All residents in this age category were randomly allocated to two groups for participation either in a study of cardiovascular diseases (N1 = 1643, 33.7%) or in the Lausanne cohort Lc65+ study (N2 = 3236, 66.3%), which resulted in a selection by simple random sampling for each of these two studies. Of the 3236 Lausanne residents randomly allocated to the Lc65+ study, 36 (1.1%) individuals living in an institution were excluded, 144 (4.5%) persons were further excluded on the basis of an updated list issued by the Population Office in 2004 (dead or moved away from Lausanne) and 3056 residents were considered eligible for contact by mail.

In March 2004, all selected individuals received a support letter from the Surgeon General of the Canton of Vaud, followed one week later by a mailing including a presentation of the study, an initial self-administered questionnaire and a stamped return envelope. Non-respondents received two follow-up mailshots with the same contents. The last mailing included an anonymous form for reporting refusals and corresponding reasons.

Out of the 3056 mailed questionnaires, 2096 (68.6%) responses were registered; 1567 (74.8%) persons agreed to participate and 529 (25.2%) refused. Compared to non-respondents or refusers, participants did not differ in gender (41.3% men in participants versus 41.4% in non-participants, $\chi^2$ test p = 0.9) or in birth year distribution (in men: 1934 18.1% versus 18.6%, 1935 22.3% versus 19.8%, 1936 20.2% versus 22.5%, 1937 19.9% versus 16.5%, 1938 19.5% versus 22.5%, $\chi^2$ test p = 0.3/in women: 1934 21.1% versus 19.9%, 1935 20.3% versus 20.1%, 1936 20.4% versus 18.8%, 1937 17.9% versus 20.8%, 1938 20.2% versus 20.4%, $\chi^2$ test p = 0.6). Participants' socio-economic characteristics closely reflected the Lausanne general population in the same age category in aggregate statistics from the Population Office (proportions of foreign nationality, distribution of marital status) or from the 2000 Swiss national population census (nationality, marital status, place of birth, living arrangement, professional activity – data not shown). Refusals

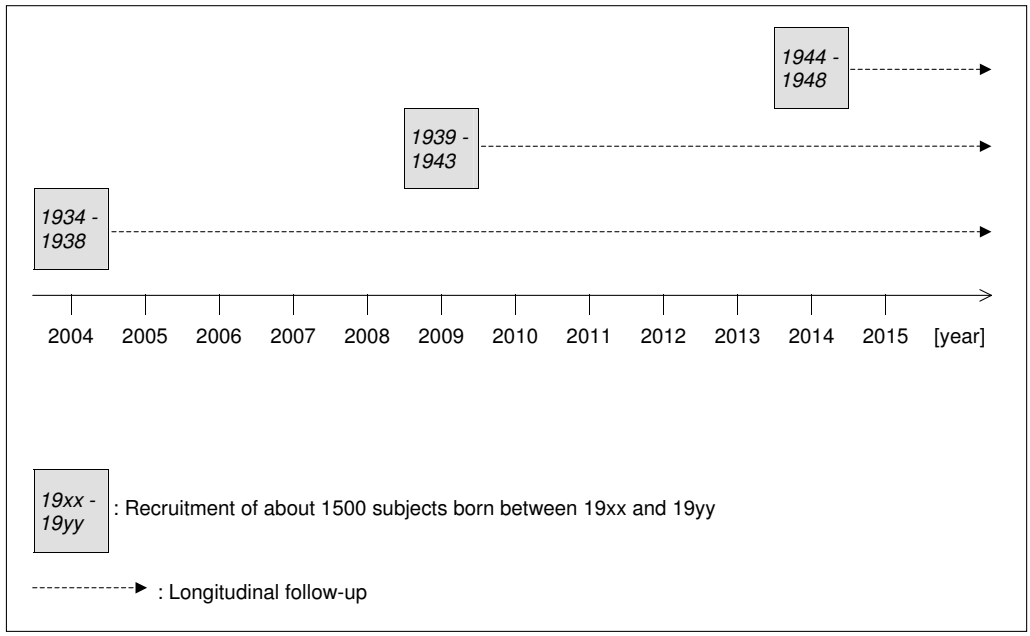


**Figure 1**
General design of the Lausanne cohort Lc65+ project 2004–2015.

were mostly motivated (multiple reasons possible) by a general disinclination to participate in any survey (57.8%), or to agree to follow-up contacts (53.9%); 24% of refusers considered that some questions intruded on their privacy, 17.8% did not have the time or lacked interest in the study topic, 17.0% refused to participate in a non-anonymous data collection. Some 10.6% indicated language limitations, 7.8% expressed difficulty in understanding questions and the same proportion attributed their refusal to poor health.

Of the 1567 respondents to the initial questionnaire, 3 subjects were later considered as ineligible (incorrect address in 2004), leaving 1564 valid observations. In 2005, all participants were invited to complete the baseline survey; 1524 (97.4%) were still eligible; 1422 (93.3%) participated in the assessment and 1416 could be classified as non-frail, pre-frail or frail according to the Fried et al. phenotype [15].

An additional sample of 100 residents born in 1933 was selected in 2004, following the same rules and process, for the piloting of questionnaires as well as in-person interviews and performance tests conducted by medical research assistants.

### *Baseline assessment in 2004–2005*

Baseline data are collected using a two-steps procedure involving a self-administered mailed questionnaire at recruitment, followed by an in-person interview at the study center with anthropometric measurements and performance tests performed by trained medical assistants. Table 1 summarizes the contents of the Lc65+ baseline assessment.

#### *Initial questionnaire (2004)*

The initial questionnaire has been designed to enable comparisons to be made with other major population-based health surveys conducted in Switzerland and Europe. Questions included batteries already used in the Swiss health surveys (Federal Office for Statistics), in the MONICA study [62] or in the SHARE European survey [43]. The instrument was pre-tested first on a convenience sample of 9 volunteers and then on 42 randomly selected subjects born in 1933. Contents emphasized life history, with indications of socio-economic status and main medical diagnoses in childhood and adulthood, and current health. As events from the past are liable to be remembered imperfectly [63], the questionnaire was organized in chronological sections from childhood to current health status in order to enhance recall.

#### *Completion of baseline data collection (2005)*

The 2005 assessment was performed according to a standardized protocol by medical research assistants supervised by a senior psychologist, after two weeks of specific training at the study center followed by a pre-test on the pilot random sample of subjects born in 1933. A self-adminis-

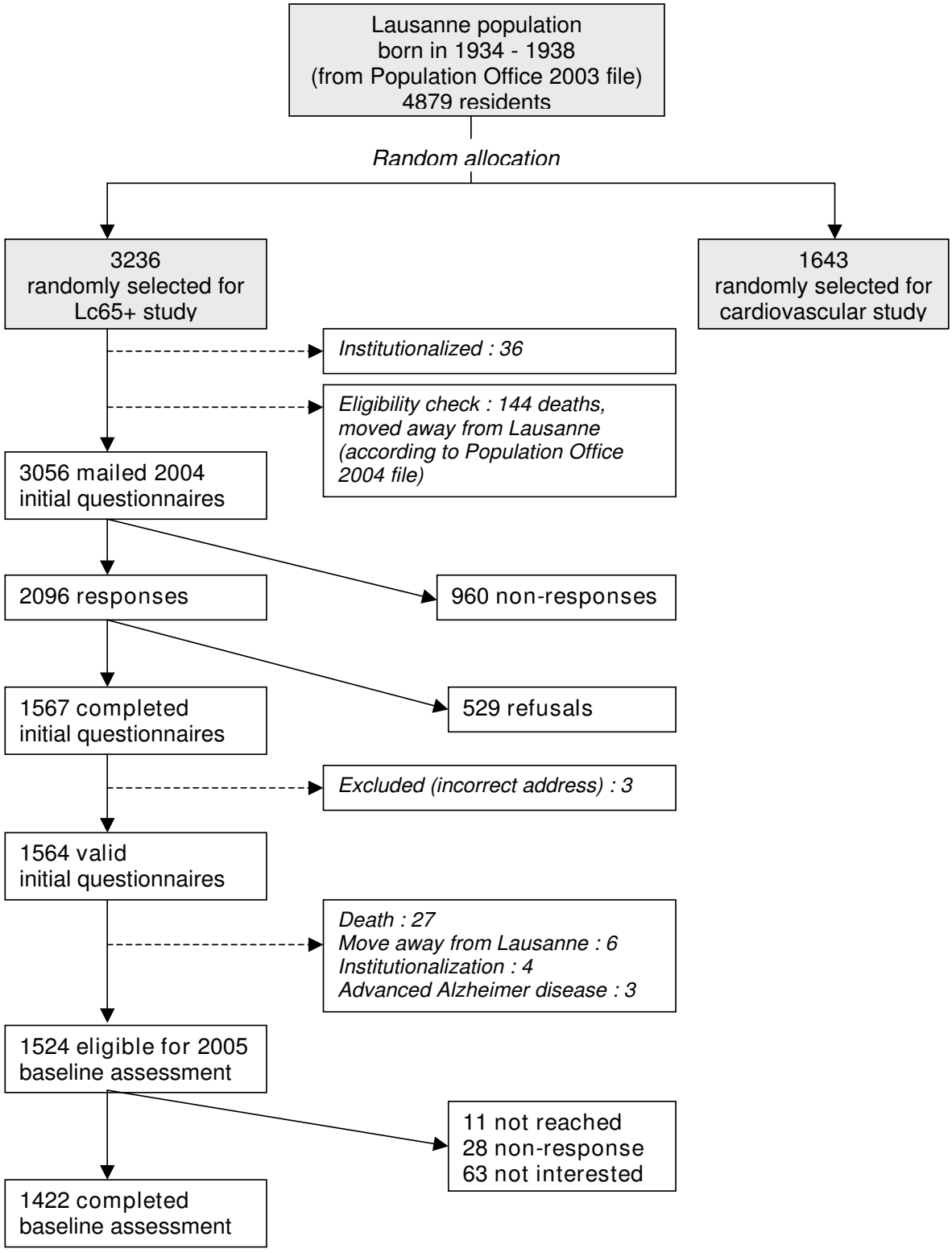


**Figure 2**
Lausanne cohort Lc65+ Study recruitment flowchart.

**Table 1: Contents of Lausanne cohort Lc65+ Study 2004–2005 baseline data collection.**

| |
|---|
| **Self-completed questionnaire** |
| - Childhood history: premature birth and birth weight category, family size at birth and at the age of 10, economic environment at birth and change in childhood, major diseases and injuries, stressful life events during infancy and early adolescence |
| - Socio-economics: country of birth, nationalities, achieved education, type and duration of professional activity, current working activity and circumstances of retirement; current subsidized health insurance as an indicator of low income, stressful life events in adulthood, marital status, number of children, size and composition of household |
| - Subjective health (WHO formulation) absolute and relative to contemporaries; perception of own aging; fear of disease, weakness, sleep perturbation, according to questions extracted from Swiss Health Surveys; sight and hearing impairments; medical diagnoses, chronic symptoms |
| - Screen for mental health and depression (GHQ-12) [33,34] |
| - Health-related behaviors: current physical activity, decrease in physical activity in past twelve months, smoking history, alcohol consumption (WHO Audit-C) [35,36] |
| - Screen for difficulty and dependence in basic and instrumental activities of daily living |
| - Current height and weight, weight 5 years ago, unintentional weight loss |
| - Falls, fear of falling and impact on activities, falls efficacy (FES-I) [37] |
| - Stressful life events in past 12 months (GALES Part I: list of events) [38] |
| **Interview** |
| - Stressful life events in past 12 months (GALES Part II: level of stress and feelings) [38] |
| - Nutrition (MNA [39-41], completed by questions on nutritional habits developed in the Canadian NuAge project [42]) |
| - Health services utilization in past twelve months (as assessed in SHARE) [43] |
| - Self-assessment of the economic situation |
| **Measurements** |
| - Weight and height |
| - Arm, waist, hip, and calf circumferences; biceps, triceps and supra-iliac skinfolds (GPM® caliper) |
| - Resting blood pressure and heart rate (measured three times at 5–10 minute intervals on right arm, OMRON® digital automatic blood pressure monitor, manually in case of rhythm abnormalities) |
| **Performance tests** |
| - Grip strength test on the right hand (Baseline® hydraulic dynamometer three measurements) [44-46] |
| - Moberg Picking-Up Test on dominant hand [47] |
| - Balance tests (10 seconds side-by-side, semi-tandem and tandem standing with open eyes according to the protocol of EPESE, 1 minute side-by-side standing, open and closed eyes) [48] |
| - Timed Up-and-Go test [49-51] |
| - Self-selected walking speed (20 meters walk single task, double task: walk and backward count, double task: walk and water glass, triple task: walk, backward count and water glass) [52-54] |
| - Timed five chair rises |
| - Cognition test (MMSE) [55], frontal and temporo-parietal functioning (Clock Drawing Test) [56-58]. If MMSE ≥ 24: verbal fluency (fruit and vegetables in one minute) [59], Trail Making Test parts A and B [60,61] |

tered questionnaire was sent to the subjects' homes prior to the appointment and responses were checked for coherence and completeness by the medical assistants. Dimensions, instruments and tests included in interviews and examinations are detailed in Table 1. Finally, participants were asked to sign informed consent forms for continuing follow-up and for linking data collected in the Lc65+ with death and hospital discharge statistics.

*Frailty assessment*

Frailty was assessed at baseline according to the five characteristics (shrinking, weakness, exhaustion, slowness and low activity) included in the frailty phenotype described by L. Fried et al.; Table 2 summarizes how each characteristic was operationalized in the Cardiovascular Health Study [15] and in the Lc65+ study.

### *Follow-up*

The Lc65+ follow-up includes an annual self-administered questionnaire (or an interview questionnaire in case of deteriorated health or cultural circumstances). Mailed questionnaires also apply to individuals who moved away from the study area, where these can be located. In addition, subjects are submitted every third year to an interview and an examination performed at the study center, replicating physical and mental performance tests already included in the baseline data collection. This follow-up process monitors all subjects until death, refusal, loss to follow-up, long-term residence in a nursing home of subjects with cognitive impairment that precludes them from responding, or hospice care. Specific problems such as impaired vision or home confinement are resolved by adapting the data collection process (e.g. phone interviews rather than mailed questionnaire, home visit rather than appointment at the study center). Furthermore, with the written consent of participants, a passive follow-up will be organized (file linkage with death certificates, possibly with hospital discharge records if feasible) until death or refusal. At all steps of recruitment and follow-up, non-responders are re-contacted by various ways (phone, mail). Where necessary, details of two relatives or friends obtained on recruitment in order to facilitate follow-up

**Table 2: Operationalization of frailty characteristics in the Cardiovascular Health Study (CHS) [15] and in the Lausanne cohort Lc65+ Study.**

| | Criteria | |
|---|---|---|
| | **Cardiovascular Health Study** | **Lausanne cohort Lc65+ Study** |
| **Characteristic of frailty** | | |
| Shrinking | Unintentional weight loss >10 lbs in prior year | Any reported unintentional weight loss in prior year |
| Weakness | Grip strength: lowest 20% by gender and body mass index | Grip strength: application of CHS gender and body mass index specific cut-off values |
| Poor endurance, exhaustion | Exhaustion self-report: responds *a moderate amount of the time* or *most of the time* to either statement "I felt everything I did was an effort" or "I could not get going" in the last week | Exhaustion self-report: responds *much* to "Did you have feelings of generalized weakness, weariness, lack of energy in the last four weeks?" |
| Slowness | Walking time/15 feet: slowest 20% by gender and height | Walking time/20 meters: application of CHS gender and height specific cut-off values |
| Low activity | Physical activity self-report: lowest 20% Kcals/week expenditure, by gender, estimated from the short version of the Minnesota Leisure Time Activity questionnaire | Physical activity self-report: less than 20 minutes of sport activity once a week and less than 30 cumulated minutes walk per day 3 times a week and avoidance of stairs climbing or light loads carrying in daily activities |
| **Classification of frailty** | | |
| Non-frail or robust | 0 criterion present | 0 criterion present |
| Intermediate, possibly pre-frail | 1–2 criteria present | 1–2 criteria present |
| Frail | 3–5 criteria present | 3–5 criteria present |

contacts can be used to reach the cohort members. Inactive addresses are checked with the Population Office.

Of 1422 participants enrolled in the Lc5+ study in 2005, 1344 (94.5%) returned completed questionnaires in 2006, 18 had died, entered institutions with impaired cognitive functions, moved away permanently or were away from Lausanne for a prolonged period; 2 subjects could not be found in spite of a valid address, 17 could not participate this year but did not retire from the cohort, and 41 asked to quit the study. In 2007, 1309 (92.1% of 2005 participants) returned their completed questionnaire; 19 had died, 17 had moved away from Lausanne and 5 had entered an institution with cognitive problems.

*Outcomes*

The annual follow-up basically purports to study outcomes such as self-rated health, morbidity, reduced activity, functional decline in instrumental and basic activities of daily living, health services utilization and death. In addition, interviews and examinations performed every third year are designed to study the health-related quality of life, objective changes in physical and mental health performance, as well as changes in dimensions of the frailty phenotype.

The 2006 and 2007 self-administered follow-up questionnaires covered:

- subjective health, fear of disease, weakness, sleep perturbation, screen for depression;

- medical diagnoses and treatments in past 12 months;

- chronic disturbing signs and symptoms lasting more than 6 months;

- current drugs;

- stressful life events in the past twelve months;

- unintentional weight loss, falls, fear of falling in the past 12 months;

- physical activity, changes in physical activity in the past 12 months;

- current difficulties/impairments in mobility tasks;

- current difficulties or help received for health-related reasons in Katz' BADLs and in Lawton IADLs;

- pain limiting activities in the past 4 weeks;

- medical visits, emergency room consultations, hospitalizations, home care and help in the past 12 months;

- current paid and unpaid work.

Yearly follow-up questionnaires also enable additional dimensions to be investigated or selected dimensions to be explored in more depth. The 2006 questionnaire integrated an assessment of the social network (abbreviated version of LSNS II [64,65]; items from the MOS Social Support Survey [66]). In 2007, participants in the Lc65+ study were asked to fill out a complementary questionnaire on sexuality in order to explore relationships with health; owing to the sensitive nature of this domain, this questionnaire was presented as optional.

In 2008, the first triennial follow-up interview and examination of the data collection in progress covers the same contents as the 2005 baseline, with some elements added from the annual self-administered questionnaires (e.g. detailed information on mobility and ADL difficulties). An assessment of health-related quality of life based on a standardized instrument (MOS SF-12) was also added, while information collected on nutritional habits and on stressful life events have been slightly simplified.

#### *Data check and analyses*

All questionnaires, interview and examination forms are first checked by a trained researcher. The quality of data entry is systematically verified to detect errors. Analyses will combine retrospective (e.g. for the study of early life experiences as risk factors for frailty), cross-sectional (e.g. for the study of relationships between contemporaneous measurements of a frailty phenotype and mental performance included in baseline data collection) and prospective (for a majority of research questions, e.g. concerning the predictors of frailty or the outcomes of frailty) approaches. The variety of dimensions included in the Lc65+ study will enable us to control for a wide range of factors in analyses or multivariate models.

At baseline, in the Lc65+ study, the estimated proportions for non-frail, intermediate (possibly pre-frail) and frail subjects were 71.1%, 26.4%, and 2.5%, respectively, in 1283 subjects with complete information on all five dimensions in the frailty phenotype defined by L. Fried et al. Applying rules used in the Cardiovascular Health Study, in which subjects considered as evaluable for frailty had three or more non-missing frailty components among the five criteria [15], 1416 subjects were classified as non-frail (71.6%), intermediate, possibly pre-frail (26.3%) or frail (2.3%).

## Discussion

In the past 50 years, persons aged 80+ have been the fastest growing segment of the population in Switzerland. The current very old population was born before 1928 and its growth has hitherto essentially been due to gains in life expectancy observed throughout the 20th century. We already face difficulties in organizing and financing the resource-intensive care associated with this age. According to conservative demographic projections, the number of Swiss residents aged 80+ will peak in 2050 [66]. This trend is common to most industrialized countries. Understanding the frailty process and specific health characteristics of cohorts born just before, during and after the Second World War is crucial to prevent their evolution towards increasing frailty and disability. Most evaluations of preventive actions (e.g. home visits) pointed to a greater effectiveness in less dependent subjects [68-70], suggesting that interventions in pre-dependent, frail individuals is probably an appropriate strategy.

To our knowledge, the Lc65+ is the first cohort specifically designed to study the frailty process in the general population with an emphasis on the youngest old. The low proportion of frail individuals at recruitment confirms the potential of this cohort for studying the occurrence and the evolution of frailty from its initial manifestations. Consequently, it will provide innovative longitudinal data on which to build the multidisciplinary research required to elaborate preventive interventions targeting frail individuals. A prospective design is necessary to disentangle the respective contributions of all medical and psychosocial characteristics encompassed within the frailty concept, study the temporal sequence of mental and physical loss of homeostasis in the frailty process, and distinguish elements that act as risk factors, determinants and facilitators in order to define appropriate interventions. A cohort design is also the only method providing accurate information concerning the impact of frailty on later outcomes such as the development of functional dependence.

The strong methodological design, the inclusion of a broad range of dimensions and risk factors, the successful enrollment – and, so far, retention strategies – are strengths of the Lc65+ project, which will make a substantial contribution towards clarifying the causal pathways leading from health to frailty and to disability.

## List of abbreviations used

ADLs: Activities of daily living; BADLs: Basic activities of daily living; EPESE: Established populations for epidemiologic studies of the elderly; FES-I: Falls efficacy scale - International; GALES: Geriatric adverse life events scale; GHQ-12: General health questionnaire-12; IADLs: Instrumental activities of daily living; LSNS II: Lubben social network scale II; MNA: Mini nutritional assessment; MONICA: Monitoring of trends in cardiovascular diseases; NuAge: Study on nutrition as a determinant of successful aging; MMSE: Mini-mental state examination; MOS: Medical outcome study; MOS SF-12: Medical outcome study – Short form 12; SHARE: Survey of health, aging and retirement in Europe; WHO Audit-C: World

health organization Alcohol use disorders identification test – C.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

BSE, principal investigator, drafted the manuscript, initiated the Lc65+ study and is responsible for its design, conduct and analysis. AK, psychologist, participates in the selection of study instruments in the domain of mental health and life events and is responsible for the data collection and the supervision of medical assistants. LSB, physician, participates in the supervision of medical assistants and in data analyses. JS, statistician, is in charge of the Lc65+ study database, conducts and supports data analyses. As members of the Lc65+ study committee, CB, JC, AP, NR, PV and GW are involved in the development of the study, obtaining research funding and selecting instruments. All authors participated in the critical revision of this manuscript.

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# 11 Annex 2

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# ALCOHOL USE AND FRAILTY IN COMMUNITY-DWELLING OLDER PERSONS AGED 65 TO 70 YEARS

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**Abstract:** *Background:* Alcohol use has beneficial as well as adverse consequences on health, but few studies examined its role in the development of age-related frailty. *Objectives:* To describe the cross-sectional and longitudinal association between alcohol intake and frailty in older persons. *Design:* The Lausanne cohort 65+ population-based study, launched in 2004. *Setting:* Community. *Participants:* One thousand five hundred sixty-four persons aged 65-70 years. *Measurements:* Annual data collection included demographics, health and functional status, extended by a physical examination every 3 years. Alcohol use (AUDIT-C), and Fried's frailty criteria were measured at baseline and 3-year follow-up. Participants were categorized into robust (0 frailty criterion) and vulnerable (1+ criteria). *Results:* Few participants (13.0%) reported no alcohol consumption over the past year, 57.8% were light-to-moderate drinkers, while 29.3% drank above recommended thresholds (18.7% "at risk" and 10.5% "heavy" drinkers). At baseline, vulnerability was most frequent in non-drinkers (43.0%), least frequent in light-to-moderate drinkers (26.2%), and amounted to 31.9% in "heavy" drinkers showing a reverse J-curve pattern. In multivariate analysis, compared to light-to-moderate drinkers, non-drinkers had twice higher odds of prevalent (adjOR: 2.24; 95%CI:1.39-3.59; p=.001), as well as 3-year incident vulnerability (adjOR: 2.00; 95%CI:1.02-3.91; p=.043). No significant association was observed among "at risk" and "heavy" drinkers. *Conclusion:* Non-drinkers had two-times higher odds of prevalent and 3-year incident vulnerability, even after adjusting for their baseline poorer health status. Although residual confounding is still possible, these results likely reflect a healthy survival effect among drinkers while those who experienced health- or alcohol-related problems stopped drinking earlier.

**Key words:** Alcohol, frailty, vulnerability.

## Introduction

Excessive alcohol drinking is detrimental to physical and mental health (1-3), and increases the risk of cancer, even at levels below those typically associated with alcohol abuse or dependence. On the other hand, moderate drinking decreases the risk of coronary heart disease, with a J-shape relationship between alcohol consumption and cardiovascular mortality (4). In older persons, the threshold between benefits and risks is of particular concern because age-related changes and potential interaction with drugs make them more vulnerable to adverse events from relatively low levels of alcohol intake (5, 6). A specific concern relates to the potential consequences of alcohol on the development of age-related frailty.

Frailty is an insidious condition of increased vulnerability to adverse outcomes. Its most widely used definition, the frailty phenotype proposed by Fried and colleagues, assesses impairment in five domains: nutrition, endurance, physical activity, muscle strength and walking (7). Frailty is defined along a continuum, with individuals meeting one or two criteria classified as pre-frail, and those with three or more criteria classified as frail. Both frail and pre-frail individuals have been shown to experience more frequent adverse outcomes, in particular disability and mortality, and thus can be considered as vulnerable (7).

Given the existing association between alcohol use and adverse health outcomes, as well as the relation between comorbidity, frailty, and adverse health outcomes, one can hypothesize a similar relationship between alcohol consumption and frailty. Surprisingly, only two studies to date gave some insight into this association. In the 3-City study, current drinkers were most frequent in non-frail participants, but the analyses did not take potential confounders into account (8). In the Women's Health Initiative, moderate alcohol intake, as compared to abstinence, lowered by about 20% the risk of developing frailty over the next 3 years (9). Given the paucity of data, we aimed to investigate the independent association between alcohol consumption and prevalent as well as incident frailty in community-dwelling older persons aged 65 to 70 years. Study hypotheses were that older persons who do not currently drink alcohol and those with high alcohol intake will both be more likely to be frail (prevalent frailty) as well as to become frail (incident frailty).

## Methods

The design of the Lausanne cohort 65+ study has been previously published (10). Briefly, 1564 randomly selected community-dwelling persons aged 65 to 70 years, living in the city of Lausanne, were enrolled in 2004 (Figure 1). Follow-up consisted of yearly self-completed questionnaires with additional in-person interview and physical assessment at 3-

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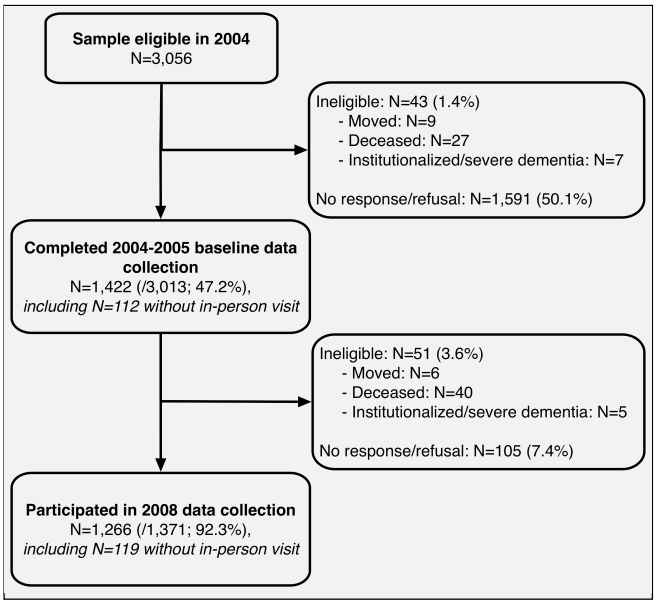
years intervals after baseline.

**Figure 1**
Flow-chart of the Lc65+ study




***Baseline data collection***

In 2004, participants completed a questionnaire that included data about demographics, education, lifestyle habits, health and functional status (11, 12). Alcohol use was measured through the AUDIT-C (13). In 2005, 1422 subjects participated in a face-to-face interview with baseline physical examination and performance tests, including tests of gait and balance, and cognition (14). Frailty was assessed using Fried's frailty phenotype (7).

***Follow-up data collection***

In 2008, assessments of alcohol intake (AUDIT-C) and frailty (Fried's criteria) were repeated in 1147 participants.

Deaths were ascertained using the local population register.

Alcohol intake was again assessed as part of the 2011 follow-up. At this time, a set of questions were added in order to identify ex-drinkers: participants who reported no alcohol use were asked about past alcohol consumption, and, if appropriate, when and why they did stop drinking.

***Operationalization of the alcohol variable***

The average number of standard drinks (wine, beer, spirits) consumed per week was estimated using the first and second questions of the AUDIT-C. Answers to the question "How many drinks containing alcohol do you have on a typical day when you are drinking?" were modified to get more precise estimation about intake (1, 2, 3-4, 5-6, 7-9, 10+ drinks). The AUDIT-C also assesses the frequency of binge drinking, defined as 6+ drinks on one occasion.

As detailed in Table 1, alcohol intake was categorized into "none", "light-to-moderate", and "excessive", based on published recommendations regarding safe alcohol consumption (15-17). "Light-to-moderate" drinking was defined as to meet the usual recommendation of at maximum 1 drink per day in women and 2 drinks per day in men. "Excessive" drinking corresponded to any consumption beyond recommended thresholds, and was further classified into two sub-categories: "at risk" and "heavy". The threshold separating "at risk" from "heavy" drinking (Table 1) was defined based on cut-offs used in similar studies (≥12 drinks/week and/or binge drinking ≥1x/month for women, and ≥20 drinks/week and/or binge drinking ≥1x/week for men) (18-20).

***Frailty assessment and definition of vulnerability***

Frailty was measured according to the following criteria, showing slight differences in the operationalization of 3 out of

**Table 1**
Definition of drinking groups

| Drinking groups | | Alcohol intake (drinks per week) | | Frequency of binge drinking (6+ drinks in one occasion) |
|---|---|---|---|---|
| Not drinking | | - | and | - |
| Light-to-moderate drinking | Women | 1-7 | and | never |
| | Men | 1-14 | and | never or <once a month |
| | | **Excessive drinking :** | | |
| At risk drinking | Women | 1-7 | and | <once a month |
| | | or 8-11 | and | never or <once a month |
| | Men | 1-14 | and | once a month |
| | | or 15-19 | and | <once a week |
| Heavy drinking | Women | ≥ 12 | or | ≥ once a month |
| | Men | ≥ 20 | or | ≥ once a week |

the 5 Fried's criteria (7):

- Low muscle strength: cut-off for low grip strength used in Fried et al.
- Poor nutrition: self-reported unintentional weight loss during last 12 months
- Poor endurance: self-reported lack of energy and fatigue during last 4 weeks
- Slow walking: cut-off for slow gait speed used in Fried et al.
- Low physical activity: defined as doing less than 20 minutes of sports per week, and walking less than 90 minutes per week. Participants fulfilling these criteria were nevertheless considered active if they reported a high amount of daily usual physical activity such as climbing stairs, or lifting weights.

Based on these five criteria, three categories are usually defined: robust (0 criterion), pre-frail (1-2 criteria), and frail (3+ criteria). For the purpose of the present study, frail (2.3%) and pre-frail (26.1%) participants were merged into a single "vulnerable" category (1+ criteria), all other participants being considered as "robust" (0 criterion).

***Statistical analyses***

Bivariate associations between categories of alcohol intake and health variables were examined using the chi-squared test and analysis of variance for categorical and continuous variables, respectively. Multivariable analyses of the cross-sectional association between alcohol intake and frailty were then performed, using the "light-to-moderate" drinkers as reference group and adjusting for potential confounders. As men and women displayed different patterns of alcohol consumption and frailty status, multivariate models were repeated separately for men and women. Significance of a gender-alcohol interaction was also tested.

The prospective relation between baseline alcohol intake and incident vulnerability among participants who were robust at baseline was investigated using a similar multivariate model that further adjusted for significant changes in alcohol consumption between 2005 and 2008. Significant changes in alcohol intake were defined as moving from "not drinking" to "at risk" or to "heavy", or from "light-to-moderate drinking" to "heavy" (increase), while reverse changes defined significant decrease in alcohol intake.

Finally, descriptive statistics were performed on data collected in 2011 about past alcohol consumption and reasons for stopping.

Analyses were conducted using Stata, version 11.0.

## Results

At baseline, complete data on alcohol-related variables were available for 1437 of the 1564 (91.9%) participants. Overall, 92.9% of men and 83.4% of women did report some consumption of alcohol over the previous 12 months. Table 2 shows baseline characteristics of participants, as well as their comparisons across the four drinking categories. Only 13% of the participants did not drink alcohol, 57.8% were light-to-moderate drinkers, and 29.2% were excessive drinkers (18.7% "at risk" and 10.5% "heavy"). Comparisons across the four drinking groups showed increasing proportions of men, as well as of current smokers as alcohol intake increased. Non-drinkers displayed the highest proportion of poor self-rated health, comorbidity, functional impairment, and previous alcohol-related problems. A similar pattern, although less pronounced, was observed in heavy drinkers. Cognitive impairment was rare altogether (2.8%), but significantly more frequent in non-drinkers.

Overall, 28.4% of the participants were considered as vulnerable. The prevalence of vulnerability was highest among non-drinkers (43.0%), and second highest in heavy drinkers (31.9%). Figure 2a displays the prevalence of vulnerability across the four drinking categories, stratified by gender. The bivariate association between alcohol intake and vulnerability displayed some reverse J-curve pattern, more pronounced in women than in men.

In multivariate analysis that adjusted for baseline differences in health status as well as other potential confounders (Table 3), non-drinkers had twice higher odds (OR: 2.24; 95%CI: 1.39-3.59; p<.001) of prevalent vulnerability than "light-to-moderate" drinkers. Heavy drinkers also had higher odds of prevalent vulnerability, but the difference did not reach statistical significance. Results were comparable when separate models were performed for men and women, and there was no significant alcohol-gender interaction, so that results are presented without gender stratification. Alcohol consumption between 2005 and 2008 remained similar in 75% of non-drinkers and 85% light-to-moderate drinkers. In contrast, about 40% of excessive drinkers decreased their alcohol consumption and were classified in lower category of intake in 2008 (data not shown).

Among the 1016 robust participants in 2005, 840 (82.7%) had frailty status assessed in 2008, among whom 220 (26.2%) were classified as vulnerable. The proportion of robust participants at baseline who transitioned toward vulnerability was highest among those who did not drink at baseline (Figure 2b).

The prospective association between alcohol intake and 3-year incident vulnerability was examined in a multivariate analysis (Table 3). Compared to light-to-moderate drinkers, non-drinkers had twice higher odds (adjOR: 2.00, 95%CI: 1.02-3-91; p=.043) of incident vulnerability after adjusting for potential confounders and significant changes in alcohol use. At risk drinking was also associated with a similar trend for increased vulnerability, although it did not reach statistical significance. In contrast, heavy drinkers had no increase in their odds of becoming vulnerable. Of note, no significant association was observed between changes in alcohol intake during the follow-up period and incident vulnerability in the multivariate models.

**Figure 2a**
Prevalence of vulnerability according to alcohol intake, by gender

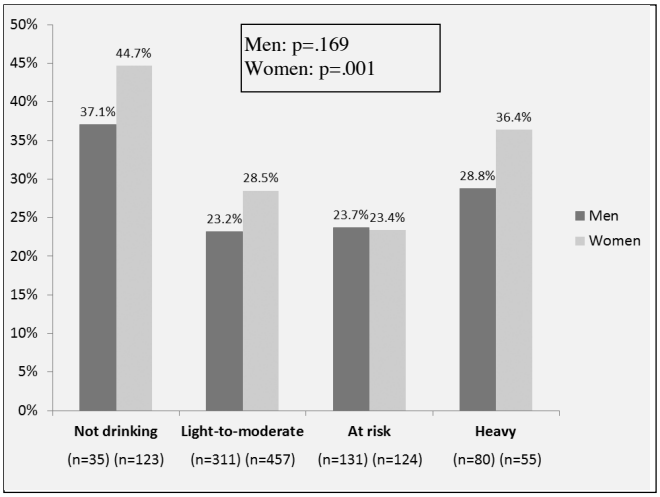
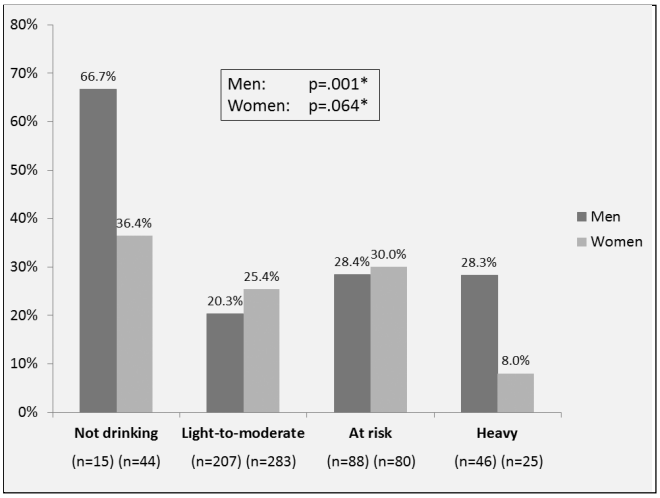



**Figure 2b**
Three-year incidence of vulnerability in initially robust participants, by gender, according to baseline alcohol intake




*Results from Chi-squared test

Follow-up over 6 years revealed that 130 participants died, with death rates of 11% among non-drinkers, 7% among light-to-moderate drinkers, 11% and 15% among "at risk" and "heavy" drinkers, respectively. This relationship between alcohol consumption and death followed a pattern similar to the association between alcohol use and frailty.

Finally, analysis of current non-drinkers in 2011 (N=70) showed that 43 were ex-drinkers. Among them, 18 did stop because of health problems, and 10 because of alcohol-related problems. Interestingly, never drinkers (n=27) tended to report a higher occurrence of significant health problems during childhood. In contrast, ex-drinkers were quite similar to long-term abstainers regarding the prevalence of comorbidity, poor self-rated health or baseline vulnerability (data not shown).

## Discussion

This study contributes to the rare data on the cross-sectional and prospective association between alcohol intake and frailty by quantifying the strength of this association at different levels of alcohol consumption. Contrary to our hypothesis of a J-shape association, results rather points to a reverse J-shape relationship, stronger in non-drinkers than among excessive drinkers. Notably, non-drinkers had a two-fold higher risk of 3-year incident vulnerability than light-to-moderate drinkers, even after taking into account their poorer health status at baseline.

This finding might reflect a beneficial effect of light-to-moderate alcohol consumption on the development of frailty, as it has been reported on the incidence of functional limitations (21, 22). Alternatively, this result might be explained by the so-called "sick quitter" effect, i.e. abstinent older persons abandoning alcohol use because of health problems. Supplementary analysis of 2011 data supports this hypothesis in showing that both long-term abstainers and quitters had poorer health indicators than current drinkers. Overall, it is likely that both a "sick quitter" bias and a beneficial effect of alcohol might coexist to explain these results.

This study extends findings reported by the Women's Health Initiative which showed that women reporting moderate alcohol intake had a 20% lower risk of developing frailty or pre-frailty over the next 3 years, compared to those who did not drink (9). In our sample, as compared to abstaining, any alcohol consumption was associated with about 60%-70% reduction of the 3-year risk of vulnerability. Adjustment for a different set of confounders might partly explain differences in results (23). Alternatively, the higher effect observed in the current study might also result from a greater benefit related to a more regular and wine-based pattern of moderate alcohol consumption observed in Europe, notably in Switzerland, compared to the United States (24-26). For instance, a study conducted in the same region found that wine constituted almost three-quarters of total alcohol consumption (26). In this regard, Lc65+ participants had a very similar consumption pattern as participants of the same age enrolled in the Swiss Health Survey, among whom 17% were non-drinkers, 58% low-risk drinkers and 26% excessive drinkers (personal data). This observation further supports the assumption that the Lc65+ sample is representative of the Swiss population in this age group. Also, our results, consistent with other studies, (27, 28), indicate that alcohol intake is quite stable over time.

At the other end of the consumption spectrum, baseline vulnerability was more frequent in heavy drinkers. Those were more frequently men reporting previous alcohol-related problems, with a worse health and functional status than other categories of drinkers at baseline. However, the odds of

**Table 2**
Baseline characteristics of the population and comparisons between drinking groups

| | | Drinking groups | | | | |
|---|---|---|---|---|---|---|
| | **Total** | **Not drinking** | **Light-to-moderate** | **At risk** | **Heavy** | **P-value*** |
| | **N=1437** | **N=187** | **N=830** | **N=269** | **N=151** | |
| | **100%** | **13.0%** | **57.8%** | **18.7%** | **10.5%** | |
| Age (mean ± SD) | 67.0 ±1.4 | 67.1 ±1.4 | 67.1 ±1.4 | 66.8 ±1.4 | 66.9 ±1.4 | .156 |
| Men (%) | 42.7 | 24.1 | 40.8 | 51.7 | 59.6 | <.001 |
| Low education (%) † | 65.5 | 71.9 | 63.3 | 66.7 | 68.0 | .126 |
| Current smoking (%) | 21.1 | 16.8 | 18.1 | 24.5 | 36.7 | <.001 |
| Poor self-rated health (%) | 34.8 | 47.1 | 34.2 | 25.8 | 39.1 | <.001 |
| Comorbidity (2+ diseases, %)‡ | 49.1 | 62.4 | 47.5 | 48.1 | 44.0 | .001 |
| Cognitive impairment (%)§ | 2.8 | 7.0 | 2.1 | 2.9 | 1.7 | .015 |
| Instrumental ADLs impairment (%)\| | 15.5 | 28.3 | 13.7 | 13.7 | 14.1 | <.001 |
| Basic ADLs impairment (%)¶ | 10.8 | 19.4 | 9.5 | 7.8 | 14.1 | .001 |
| Any previous alcohol-related problem (%) | 4.6 | 13.9 | 1.7 | 4.5 | 9.9 | <.001 |

* P-value from Chi-square test (categorical variables) or ANOVA (continuous variables); † Defined as less than 12 years of education (compulsory school or apprenticeship); ‡ Defined as self-reporting 2 or more medical diagnoses out of: hypertension, coronary heart disease, other heart diseases, stroke, diabetes mellitus, chronic respiratory disease, arthritis, osteoporosis, gastrointestinal ulcer, depression, Parkinson disease and cancer; § Defined as a score <24/30 at Folstein's Mini-Mental State Examination (14); | Defined as any difficulty or need for help in Instrumental Activities of Daily Living (shopping, and performing usual household activities) (12); ¶ Defined as any difficulty or need for help in Basic Activities of Daily Living (include bathing, dressing, using the toilet, transferring into/out of bed or chair, feeding) (11)

**Table 3**
Results from multivariate analyses of the association between alcohol use and prevalent (cross-sectional analysis) and 3-year incident (longitudinal analysis) vulnerability

| **Drinking group** | **Cross-sectional analysis** | | | **Longitudinal analysis** | | | |
|---|---|---|---|---|---|---|---|
| | **AdjOR*** | **95%CI** | **P-value** | **AdjOR†** | **95% CI** | **P-value** | |
| Light-to-moderate drinking (reference category) | - | - | - | - | - | - | - |
| At risk drinking | .95 | .64 | 1.40 | .780 | 1.49 | 0.98 | 2.26 | .065 |
| Heavy drinking | 1.39 | .86 | 2.25 | .173 | 0.73 | 0.34 | 1.58 | .427 |
| Not drinking | 2.24 | 1.39 | 3.59 | .001 | 2.00 | 1.02 | 3.91 | .043 |

*adjusted for age, gender, education, current smoking, self-rated health, comorbidity (2+ self-reported medical diagnoses out of: hypertension, coronary heart disease, other heart diseases, stroke, diabetes mellitus, chronic respiratory disease, arthritis, osteoporosis, gastrointestinal ulcer, depression, Parkinson disease and cancer.), cognitive impairment, functional status (impairment in Basic respectively Instrumental ADLs), and reporting any previous alcohol-related problem; ** adjusted for age, gender, education, current smoking, self-rated health, comorbidity (2+ self-reported medical diagnoses out of: hypertension, coronary heart disease, other heart diseases, stroke, diabetes mellitus, chronic respiratory disease, arthritis, osteoporosis, gastrointestinal ulcer, depression, Parkinson disease and cancer.), cognitive impairment, functional status (impairment in Basic respectively Instrumental ADLs), and reporting any previous alcohol-related problem, as well as significant changes in alcohol intake between 2005 and 2008.

vulnerability in heavy drinkers did not remain significantly higher in cross-sectional and longitudinal multivariate analyses once controlling for these differences in baseline health characteristics. Several hypotheses might explain the absence of a significant association between a high alcohol intake and frailty. Besides the sick quitter effect, an alternative hypothesis could be that long-time heavy drinkers might die before reaching this age (healthy survivor effect), as shown in some previous study (29). The observation of higher death rates among excessive drinkers in our study during the 6-year follow-up supports this hypothesis.

Our results are also consistent with the modification of the association between alcohol use and mortality observed with age. The J-curve pattern tends to change towards a reverse J-curve, especially among persons aged over 65 years with cardiovascular risk factors (3).

This study has several strengths, including a large population-based sample of community-dwelling participants in a narrow age range, making it homogeneous and representative. Then, despite the low prevalence of frailty in this age group, we grouped frail and pre-frail category to get a sufficient sample and observed a 3-year incidence of vulnerability reaching 20%.

As a limitation, alcohol intake was self-reported using the AUDIT-C. This clinical instrument is easily administered and has been shown valid to identify at risk drinking (13), but does not allow a precise estimation of daily alcohol use in grams. Then, self-reporting implies the potential for a social desirability bias towards underreporting, even though the use of questionnaire instead of face-to-face interview likely reduced this bias. Finally, we had no information about the circumstances under which people drink. Nevertheless, these limitations are present in numerous population-based studies not focusing on alcohol use, some of which did observe strong associations between high alcohol intake and adverse health outcomes (18-19, 30).

As a conclusion, in this sample of community-dwelling persons aged 65-70 years, non-drinkers had twice higher odds of prevalent and 3-year incident vulnerability, even after adjusting for their baseline poorer health status. This finding likely results from both a "sick quitter" bias and a beneficial effect of alcohol. In contrast, almost 30% of these young-old persons drank more than recommended, and had a non-significantly increased risk of vulnerability.

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# 12 Annex 3

Seematter-Bagnoud L, Büla CJ, Santos-Eggimann B. Effect of alcohol use on gait under single and dual task in community-dwelling older persons aged 65 to 70 years. (submitted)

**« Effect of alcohol use on gait under single and dual task**

**in community-dwelling older persons aged 65 to 70 years. »**

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**Figures**: 1

**Running title**: Alcohol use and gait parameters in young-old persons

**Key words**: alcohol, gait, older persons

**Abstract**

**Background**: the association of different levels of alcohol use with gait parameters still received little attention.

**Objectives**: To describe the cross-sectional and longitudinal association between alcohol intake and gait parameters in older persons.

**Methods**: Community-dwelling persons aged 65-70 years (N=807) enrolled in the Lausanne cohort 65+ study**.** Information on health, functional status, and alcohol use was self-reported at baseline and at 3-year follow-up, while gait performance was measured under single and cognitive dual-task.

**Results**: Compared to light-to-moderate drinking, heavy drinking was associated with slower gait speed in single task (adj. coeff: -.043, 95%CI:-.0.80 to -.005, p=.025), and dual task, although this latter effect was not significant. No significant association was observed between heavy drinking and gait speed variability. Non-drinkers walked slower and with higher speed variability than light-to-moderate drinkers, both in single and dual tasks, but these associations disappeared after adjustment for comorbidity. At 3-year follow-up, 35.2% and 34.1% of the participants walked significantly slower in single and dual-task, respectively. This proportion varied only marginally across drinking categories.

**Conclusion:** At baseline, heavy alcohol consumption was significantly associated with slower gait speed in single task. Healthy survival effect probably explains why this association was not retrieved in longitudinal analyses. The observed trend of poorer gait performance in non-drinkers disappeared after adjustment for comorbidity, suggesting confounding by a worse health status.

## Introduction

The consequences of chronic alcohol abuse on gait and balance are well known, but the effects of moderate consumption on gait parameters still received little attention. Some previous studies observed that even moderate alcohol intake might affect cerebellar cells over the long term, causing ataxia and increased body sway, which may affect gait (Ahmad, Rohrbaugh, Anokhin, Sirevaag, & Goebel, 2002; Piguet et al., 2006; Rogind, Lykkegaard, Bliddal, & Danneskiold-Samsoe, 2003). However, the relationship between alcohol-related cerebellar damage and gait speed and variability remains controversial. For instance, a study performed among older adults failed to demonstrate any significant association between alcohol-related reduced cerebellar volume and features of ataxic gait (Piguet et al., 2006).

Even though moderate alcohol use might not cause gross alteration of usual gait, the effect of alcohol might become more obvious when stressors are added, such as walking under dual-task condition. Indeed, gait is a highly complex, semi-automatic motor function, which requires some amount of attentional resources (Nutt, Marsden, & Thompson, 1993; Yogev-Seligmann, Hausdorff, & Giladi, 2008). It has been shown that gait slows under dual-task condition, with increased gait variability (Yogev-Seligmann et al., 2008). This effect is more pronounced when cognition is impaired, showing the inability to allocate attention properly when performing a simultaneous cognitive task, such as counting backward while walking (Yogev-Seligmann et al., 2008). As alcohol also causes cortical brain damage, dual tasking might reveal subtle negative consequences of alcohol use in subjects who drink beyond recommended threshold, but who are not alcoholics.

On the other hand, there is some evidence that light-to-moderate alcohol use has a protective effect against vascular diseases (Di Castelnuovo et al., 2006). One could hypothesize that it

could therefore balance the potential detrimental influence of alcohol on gait, by preventing damage to cerebral circulation.

Despite the high prevalence of both gait impairment and alcohol use in older persons, we found no study that specifically investigated this relationship in this specific population. This analysis aimed to examine the cross-sectional and prospective association between different levels of alcohol use and gait parameters. The hypothesis was that drinking above recommended threshold will be associated with poorer gait performance measured over a 20-meter walk, as compared to moderate drinking that might have a protective effect. Specifically, we expected that higher alcohol consumption would be associated with slower gait speed and higher gait speed variability. The negative influence of higher alcohol intake on gait was expected to be more evident under cognitive dual-task condition. In addition, we hypothesized that controlling for comorbidity will attenuate the observed associations.

## Methods

The design of the Lausanne cohort 65+ study has been previously described (Santos-Eggimann et al., 2008). Briefly, this population-based cohort launched in 2004 enrolled 1564 randomly selected community-dwelling persons aged 65 to 70 years, living in the city of Lausanne, Switzerland.

### Data collection

In 2004, participants completed a questionnaire that included data about demographics, education, lifestyle habits, health and functional status. Alcohol use was measured using the AUDIT-C (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). In 2005, participants underwent a face-to-face interview with baseline physical examination as well as physical and cognitive performance tests, including gait analysis in a sub-sample of 807 participants.

In 2008, follow-up assessment of gait performance was available in 684 (84.7%) of the 807 participants. Deaths were ascertained using the local population register.

### Operationalization of the alcohol variable

The average number of standard drinks (wine, beer, spirits) consumed per week was estimated using the first and second questions of the AUDIT-C. As described previously (Seematter-Bagnoud, Spagnoli, Büla, & Santos-Eggimann, 2014), alcohol intake was categorized into “none”, “light-to-moderate”, “at risk” and “heavy”. “Light-to-moderate” drinking was defined according to the usual recommendation of maximum of 1 drink per day in women and 2 drinks per day in men (National Institute on Alcohol & Alcoholism, 2009). The threshold separating “at risk” from “heavy” drinking was defined based on cut-offs used in similar studies, with at risk drinking corresponding to 8-11 drinks per week in women, and 15-19 drinks per week in men, and heavy drinking encompassing any intake above these limits (Perreira & Sloan, 2002).

**Gait assessment**

Gait parameters were measured under the same conditions at baseline and 3-year follow-up, with participants walking at self-selected, usual, speed over 20 meters in a well-lit walkway. During dual task, participants were asked to count backwards aloud from fifty while walking. No instruction was given regarding prioritization of any task. Gait speed (m/s) was estimated from the angular velocity recorded by the Physilog® system, a device that includes 4 body-fixed sensors on lower limbs and a data logger carried on the waist (BioAGM, Tour-de-Peilz, Switzerland (Aminian, Najafi, Bula, Leyvraz, & Robert, 2002). Gait speed variability was assessed using the coefficient of variation (CV in %) defined as the standard deviation divided by the mean value of gait speed for each stride.

**Statistical analyses**

Characteristics of participants (including gait parameters) were compared across the categories of alcohol intake, using chi-square test for categorical variables. Kruskal-Wallis test was used for continuous variables because of non-normal distribution and the presence of outliers.

Robust linear regression analyses were performed to examine the cross-sectional association between alcohol intake and gait parameters to take heteroscedasticity into account, both in bivariate and multivariate models. As men and women displayed different patterns of alcohol consumption and gait parameters, a gender-alcohol interaction was also systematically tested in multivariate models. Other covariates included in the analyses were age, education and comorbidity (defined as self-reporting 2 or more medical diagnoses out of a list of 12).

Bivariate analyses examined the prospective association between baseline alcohol use and three-year changes in gait speed and its CV under single and dual-task conditions,

respectively. Regarding gait speed, the outcome was defined as a decline of 0.1 m/s, which is considered as a clinically meaningful change (Perera, Mody, Woodman, & Studenski, 2006). Analyses were conducted using Stata, version 13.0.

The study was approved by the Cantonal Human Research Ethical Committee, and written consent was obtained from all participants during the in-person visit.

## Results

Overall, 91.3% of the participants (mean age: 67 years, 55% women, 46% reporting more than one chronic disease, 7% reporting any impairment in basic activities of daily living) reported consuming some alcohol over the previous 12 months. Among those, two-thirds reported light-to-moderate drinking, about a fourth reported at-risk drinking, and a tenth heavy drinking (Table 1). Comparisons of baseline characteristics across drinking categories showed that non-drinkers and heavy drinkers were twice as likely to report functional impairment (14.1%, and 10.8%, respectively vs 6.1% and 7.7% among moderate and at risk drinkers, p=.073). Non-drinkers more frequently reported comorbidity (59.2% vs 40% to 45% in other categories, p=.067), and were more often cognitively impaired (5.7% vs <2% in other categories, p=.001, defined as a Mini-Mental State Examination score <24/30 (11)).

### *Baseline gait analysis*

Overall, gait speed was 1.13±0.16 m/s under single task and decreased to 0.99±0.19 m/s in dual task (counting backwards). Average gait speed variability in the entire sample was 3.5% under single task condition, and increased up to 6.2% during dual task. Comparison across categories indicated slower gait speed and higher gait speed variability among non-drinkers, as well as among heavy drinkers, but these differences were not significant in bivariate analysis (Table 1).

During dual task, the proportion of participants counting backwards without any error was 63.3% , 76.9%, 83.4% and 76.1% among non-drinkers, low-to-moderate drinkers, at risk and heavy drinkers, respectively (p=.052). The mean number of errors did not differ significantly across categories of alcohol intake.

Table 2 shows the results of the crude and adjusted models examining the cross-sectional relationship between gait parameters and alcohol intake, using the light-to-moderate drinkers

as the reference group. In bivariate analyses, the most consistent pattern was observed among non-drinkers who showed slower gait speed and increased gait variability under both single and dual-task conditions. However, these differences did not remain once controlling for comorbidity in multivariate analyses. Although heavy drinkers also presented with similarly altered gait pattern, only gait speed under single task condition was significantly reduced (adjusted coeff: -.043, 95%CI:-.0.80 to -.005, p=.025).

*Longitudinal analysis*

About 16% of subjects had no follow-up gait recording, half of them because health-related reasons precluded the performance tests. As compared to participants with follow-up measurements, they had slower gait speed at baseline (1.07 ± .17m/s vs 1.14 ± .15m/s, p<.001), as well as higher speed variability (4.1% vs 3.4%, p=.003). Over the three years of follow-up, 39 subjects died, corresponding to 8.1% of heavy drinkers vs only 2.8% of non-drinkers (p=.496). When comparing baseline and 3-year gait performance, a clinically significant decline in speed (≥0.10 m/sec) was observed in 35.2% of the subjects under single task condition. This proportion did not differ across levels of alcohol use (range: 32.8% (heavy drinkers) to 37.7% (non-drinkers), p=.690). Speed decline occurred in a similar proportion (34.1%) of participants under dual task condition. Again, no significant association was observed across drinking categories.

Gait variability also deteriorated (increase) at 3-year follow-up in 43.3% and 45.0% of participants under single and dual task condition, respectively. Figure 1 displays the proportions of participants in each drinking category with increased gait speed variability at follow-up under single and dual task conditions, respectively. These proportions were highest in non-drinkers, lowest among light-to-moderate drinkers, and increased progressively as

alcohol consumption increased. This U-shaped relationship was most apparent in single task condition, but was not statistically significant.

## Discussion

Results from cross-sectional and longitudinal analyses in this large sample of community-dwelling elderly indicate that alcohol abstention as well as excessive use were associated with poorer gait performance (slower gait speed and increased gait variability), suggesting a U-shaped relationship. However, these associations were inconstant and varied according to adjustment for health variables. Several factors might contribute to the failure of finding an independent effect of alcohol on gait measurement.

First, both non-drinkers and heavy drinkers differ from moderate drinkers in terms of health status. A previous analysis on a subgroup of abstinent participants indicated that half were ex-drinkers, most of whom stopped drinking because of health problems, while the other half were never drinkers who also had a poorer health status than moderate drinkers (Seematter-Bagnoud et al., 2014).

Second, the small number of heavy drinkers (N=58) resulted in limited statistical power, especially in longitudinal analyses. As heavy drinkers are less likely to participate into research study on health, the proportion observed in the current study probably underestimates their true prevalence. However, this proportion is very similar to those observed in other studies undertaken in Switzerland (Foerster et al., 2009). In addition, results from the longitudinal analyses were probably biased by selective attrition and a healthy survivor effect. Results showing worse gait performance at baseline (slower gait speed and increased gait variability) among participants lost to follow-up, as well as the increased death rate among heavy drinkers support this hypothesis of a healthy survivor effect. This likely resulted in underestimation of the deleterious effect of heavy alcohol intake on gait.

Another interesting finding from this study is the relatively small proportion (about a third for gait speed and a half for gait variability) of participants who had worse gait performance at 3-

year follow-up. This observation extends previous observation showing that gait speed remains relatively constant throughout adult life until age 65 where it starts to decline by 1–2% per year (.008 m/s to .03 m/s) up to 80 years (Beavers et al., 2013; Forrest, Zmuda, & Cauley, 2006; White et al., 2013). In this context, the use of the Physilog® device was useful to detect these subtle changes in gait speed and variability.

This low proportion of participants with decline in gait performance could also result from the previously mentioned healthy survivor effect. In addition, while participants were relatively young and fit, their average gait speed at baseline was at the lower end of age-specific normative values previously reported in community-dwelling older persons (Bohannon & Williams Andrews, 2011; Kenny et al., 2013).

Finally, an original contribution of this study is to show that dual tasking did not improve the detection of gait differences across drinking categories. In addition to factors previously discussed, the selection of the dual-task could explain this negative finding. Selecting a more complex and challenging cognitive task than counting backward might have provided different results.

In conclusion the negative effect of heavy alcohol consumption on gait speed was significant in cross-sectional analysis of single task. Healthy survival effect probably explains why this association was not retrieved in longitudinal analyses. The observed trend of poorer gait performance in non-drinkers disappeared after adjustment for comorbidity, suggesting confounding by a worse health status.

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**Conflict of interest**

The authors declare no conflict of interest.

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**Table 1 : characteristics of participants and comparison according to alcohol intake**

| | | Drinking groups | | | | |
|---|---|---|---|---|---|---|
| | Total | Not drinking | Light-to-moderate | At risk | Heavy | P-value* |
| | N=807 | N=71 | N=492 | N=170 | N=74 | |
| | 100% | 8.8% | 61.0% | 21.1% | 9.2% | |
| Age (mean ± SD) | *67.0 ±1.4* | *67.2 ±1.4* | *67.0 ±1.4* | *66.8 ±1.3* | *67.0 ±1.4* | *.221* |
| Men (%) | *46.3* | *25.4* | *44.1* | *53.5* | *64.9* | *<.001* |
| Low education (%) † | *64.2* | *70.4* | *62.3* | *65.7* | *67.6* | *.480* |
| Comorbidity ($2^+$ chronic diseases, %)‡ | *46.2* | *59.2* | *45.5* | *45.0* | *40.5* | *.001* |
| Cognitive impairment (%)§ | *1.9* | *5.7* | *1.6* | *1.8* | *0.0* | *.067* |
| Instrumental ADLs impairment (%)‖ | *10.5* | *16.9* | *8.5* | *12.9* | *12.2* | *.094* |
| Basic ADLs impairment (%)‖ | *7.6* | *14.1* | *6.1* | *7.7* | *10.8* | *.073* |
| Fear of falling (%) | 37.5 | 45.4 | 37.0 | 35.0 | 39.1 | *.508* |
| Single Task : walking at usual speed | | | | | | |
| - Gait speed (m/s, mean ± SD) | 1.13±.16 | 1.10±0.17 | 1.14±0.15 | 1.14±0.15 | 1.11±0.18 | .194 |
| - Gait speed CV *(%) | 3.52 | 3.58 | 3.44 | 3.30 | 3.64 | .410 |
| Dual Task : walking while counting backwards | | | | | | |
| - Gait speed (m/s, mean ± SD) | 0.99±0.19 | 0.94±0.20 | 1.00±0.19 | 1.00±0.18 | 0.97±0.20 | .061 |
| - Gait speed CV *(%) | 6.22 | 6.68 | 6.09 | 5.93 | 6.48 | .256 |

* P-value from Chi-square test (categorical variables) or ANOVA (continuous variables)

† Defined as less than 12 years of education (compulsory school or apprenticeship)

‡ Defined as self-reporting 2 or more conditions out of the following list: hypertension, coronary heart disease, other heart diseases, stroke, diabetes mellitus, chronic respiratory disease, arthritis, osteoporosis, gastrointestinal ulcer, depression, Parkinson disease and cancer.

§ Defined as a score <24/30 at Folstein's Mini-Mental State Examination

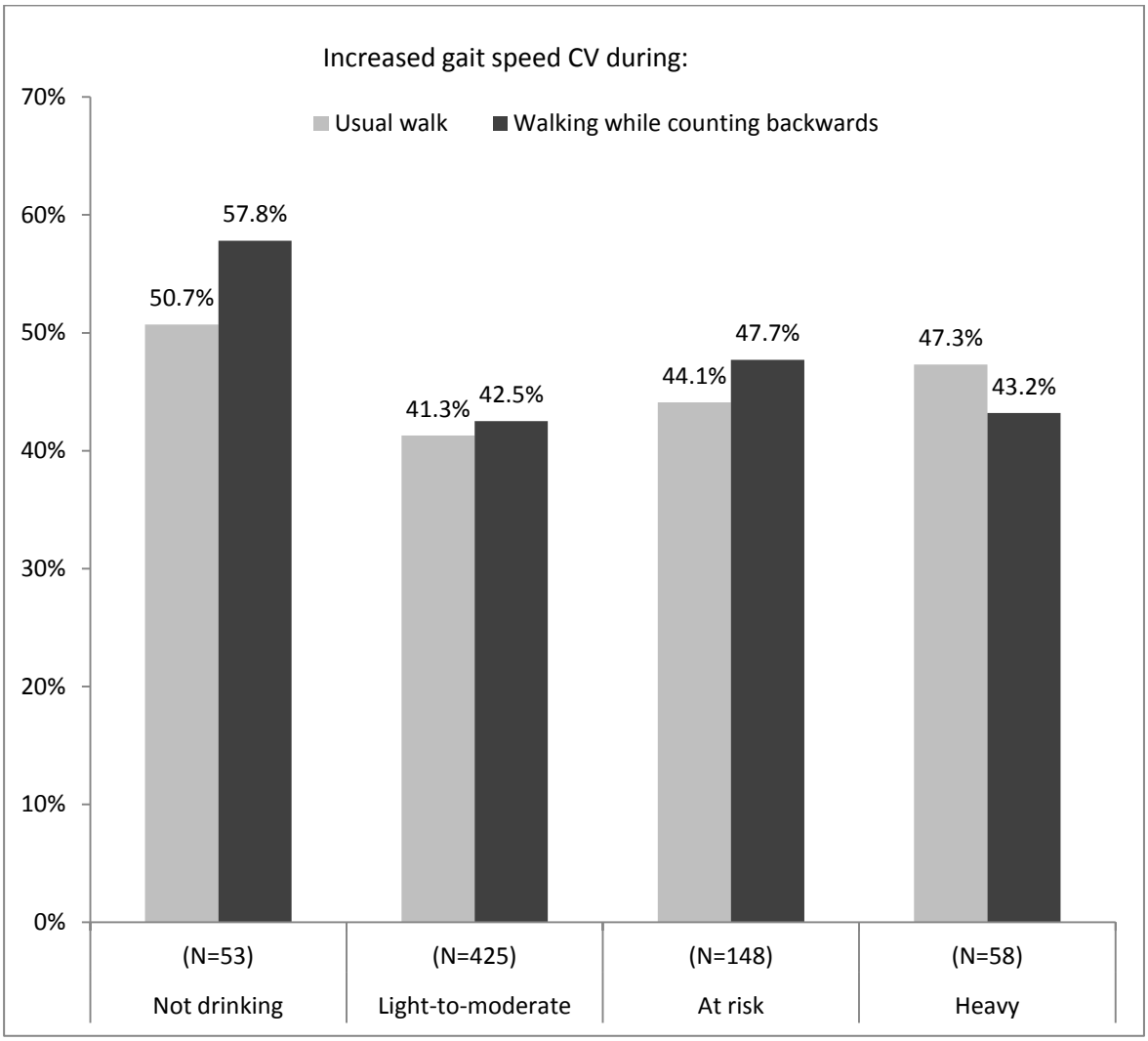
‖ Instrumental Activities of Daily Living include shopping, and performing usual household activities.Basic Activities of Daily Living were bathing, dressing, using the toilet, transferring, feeding.

**Table 2: cross-sectional association of gait parameters and alcohol intake***

| | Bivariate analysis** | | | Multivariate analysis*** | | |
|---|---|---|---|---|---|---|
| Single Task : walking at usual speed | | | | | | |
| Gait speed (m/s, positive coefficient indicating higher speed) | | | | | | |
| | coefficient | 95%CI | p-value | coefficient | 95%CI | p-value |
| No drinking | *-.035* | -.073 - .004 | .077 | *-.025* | -.063 - .013 | .201 |
| Light-to-moderate drinking | *Reference* | | | *Reference* | | |
| At risk drinking | *.002* | -.025 - .029 | .899 | *-.006* | -.033 - .020 | .652 |
| Heavy drinking | *-.032* | -.069 - .006 | .103 | *-.043* | -.080 - -.005 | .025 |
| Gait speed CV (%,positive coefficient indicating greater gait speed variability) | | | | | | |
| No drinking | *.337* | .048 - .626 | .022 | *.281* | -.010 - .571 | .058 |
| Light-to-moderate drinking | *Reference* | | | *Reference* | | |
| At risk drinking | *-.030* | -.023 - .017 | .770 | *-.020* | -.022 - .018 | .848 |
| Heavy drinking | *-.083* | -.037 - .200 | .564 | *-.030* | -.032 - .254 | .832 |
| Dual Task : walking while counting backwards | | | | | | |
| Gait speed (m/s) | | | | | | |
| | coefficient | 95%CI | p-value | coefficient | 95%CI | p-value |
| No drinking | *-.053* | -.101 - -.004 | .031 | *-.036* | -.084 - .012 | .139 |
| Light-to-moderate drinking | *Reference* | | | *Reference* | | |
| At risk drinking | *.010* | -.024 - .043 | .563 | *.003* | -.030 - .036 | .855 |
| Heavy drinking | *-.025* | -.072 - .021 | .285 | *-.036* | -.082 - .011 | .130 |
| Gait speed CV (%) | | | | | | |
| No drinking | *.621* | .004 – 1.24 | .048 | *.589* | -.039 – 1.22 | .066 |
| Light-to-moderate drinking | *Reference* | | | *Reference* | | |
| At risk drinking | *.029* | -.400 - .458 | .893 | *.001* | -.436 - .437 | .998 |
| Heavy drinking | *.420* | -.177 - 1.02 | .168 | *.383* | -.22 - .990 | .217 |

* As separate models for men and women had close results, and the test for interaction was not significant, a unique model is displayed in the table.
**Results from bivariate robust regression
*** Results from robust regression model adjusting for age, gender, education, and comorbidity

**Figure 1:** Proportion of participants with increased gait speed variability at 3–year follow-up as compared to baseline, according to alcohol intake and walking condition.



# 13 Annex 4

Seematter-Bagnoud L, Büla CJ, Santos-Eggimann B. Alcohol consumption and health services utilization in community-dwelling older persons. (submitted)

# Alcohol consumption and health services utilization in community-dwelling older persons

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## Conflict of interest

The authors declare no conflict of interest.


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**Abstract**

In a population-based sample (N=1266) of community-dwelling persons aged 65-70 years, alcohol intake was not associated with the number of hospital admissions, but had an inverse relationship with planned physician visits over five year (mean cumulative number decreasing from 34.0 in non-drinkers to 27.6, 25.9 and 25.0 in light-to-moderate, at-risk and heavy drinkers, respectively, p=.02). However, this association did not remain significant once adjusting for comorbidity and subjective health in multivariate analyses. Both the "sick quitter" and "healthy survivor" effects, as well as more health-conscious behavior among light-to-moderate drinkers, likely explain these findings.

## Background

Alcohol use impacts on health services utilization because of consequences of acute intoxication, such as accidents, as well as secondary to health problems enhanced by chronic excessive drinking (cirrhosis, stroke, depression,…). The nature of this association among older drinkers is however less clear.

A U-shaped association has been reported with the use of inpatient services: life-long abstainers and heavy drinkers are more frequent users than low drinkers (1). Abstainers might have higher utilization because of chronic conditions since childhood preventing them from drinking. At the other end of the spectrum, heavy drinkers have been shown to have increased admission rates to the emergency department (2). Interestingly, adults with alcohol consumption just above recommended levels were also shown to have higher risk of alcohol-related hospital admission (3).

By contrast, outpatient services utilization appears inversely related to the level of alcohol consumption (1, 4). In particular, preventive care use appears especially neglected in heavy drinkers compared to the more health-conscious low drinkers (5).

Given the paucity of data, this work aimed to examine the association between alcohol intake and the health services use. Specifically, the hypotheses were that alcohol use above recommended cut-off would be associated with increased hospital admissions and unplanned outpatient visits, but decreased planned outpatient visits over a 5-year period.

## Methods

The Lausanne cohort 65+ study design has been previously described(6). Briefly, this population-based cohort launched in 2004 enrolled 1564 randomly selected community-dwelling persons aged 65 to 70 years, living in the city of Lausanne, Switzerland. The baseline questionnaire included data about demographics, education, lifestyle habits, health and functional status, as well as the use of health services. Follow-up consisted in a yearly questionnaire, as well as a face-to-face interview with physical examination and performance tests every three years. Participants followed-up from 2004 to 2008 were included in this analysis (N=1266).

**Measure of alcohol use**

The average number of standard drinks (wine, beer, spirits) consumed per week was estimated using the first and second questions of the AUDIT-C(7). As previously described, alcohol intake was categorized into "none", "light-to-moderate", "at risk" and "heavy"(8). "Light-to-moderate" drinking was defined according to the usual recommendation of maximum of 1 drink per day in women and 2 drinks per day in men(9). The threshold separating "at risk" from "heavy" drinking was defined based on cut-offs used in similar studies, with at risk drinking corresponding to 8-11 drinks per week in women, and 15-19 drinks per week in men, and heavy drinking encompassing any intake above these limits.

**Information on health services use**

At each yearly follow-up, participants were asked about their use of health services over the last 12 months. Self-reported data included the number of planned and unplanned outpatient visits to a physician and the number of overnight hospital admission.

To estimate the average 5-year use of health services, the following outcomes were defined:

1) *Outpatient visits*:

- mean cumulative number of physician visits over 5 years (planned and unplanned visits separately)

2) *Hospital admission*:

- proportion of participants with at least one hospital admission over 5 years
- mean cumulative number of admissions over 5 years

**Statistical analyses**

Bivariate analyses examined the association between the level of alcohol intake and health services use outcomes. As the number of physician visits and of hospital admissions are count data with a variance exceeding the mean, zero-truncated negative binomial regression were performed to examine their association (incidence rate ratio: IRR) with the level of alcohol intake, using the "light-to-moderate" drinkers as reference group. Then, similar models were used in multivariate analyses adjusting for gender, comorbidity (2+ chronic diseases), low level of education, and poor self-rated health.

**Results**

Every year, more than 90% of the participants reported at least one outpatient visit over the previous 12-month period. Mean annual number of visits varied from 5.3 to 6.6 (median: 4) over the study period. Among participants with at least one visit, about one fourth reported at least one unplanned visit (most often 2 or 3). About one in six participants reported an acute hospital admission over the previous 12-month period, a proportion that remained stable over the 5-year follow-up period.

Overall, the mean cumulative number of planned outpatient visits was 27.8. There was a clear inverse relationship with alcohol consumption (Table 1), as visits decreased from 34.0 in non-drinkers to 27.6, 25.9 and 25.0 in light-to-moderate, at-risk and heavy drinkers, respectively (p=.02). Unplanned visits (mean cumulative number 3.0) did not follow a similar pattern, even though non-drinkers also had slightly higher use, although not significantly.

Almost half of the participants did report at least one hospitalization during the study period (mean 2.2). The proportion of persons with at least one hospital admission was slightly, although not significantly, lower among heavy drinkers. However, the mean cumulative number of hospital admissions did not vary according to alcohol intake.

In multivariate regression analyses adjusting for socio-demographic and health variables, the association between alcohol intake and outpatient physician visits did not remain significant (Table 1). Similarly, no association was observed with acute hospital admissions. In these analyses, comorbidity (adjIRR:1.58, 95%CI:1.46-1.72, p<.001) and poor self-rated health (adjIRR:1.60, 95%CI:1.56-1.77, p<.001) were both associated with increased number of

planned outpatient visits. Similar associations were observed with unplanned outpatient visits, as well as with acute hospital admissions (adjIRR ranging from 1.48 to 1.56), whereas low education was associated with decreased planned (adjIRR: 0.96, 95%CI:0.80-0.94, p<.001) and unplanned (adjIRR: 0.73, 95%CI:0.57-0.94, p<.001) physician visits.

## Discussion

In this study, alcohol consumption was associated with a weak and non significant decrease in planned outpatient visits from light to heavy drinkers. In contrast, and contrary to our initial hypotheses, results did not show any significant increase in health services use related to higher alcohol consumption. These results probably reflect the complex interplay between alcohol consumption, health status, and health related behaviors in older persons. Indeed, light drinkers have been shown to be more prone to consult for a general medical exam or preventive services, whereas heavy drinkers might neglect some health problems and ignore preventive services use (5). This hypothesis is supported by the observation that participants reporting heavy drinking did not report more comorbidity, but had poorer functional status as compared to other drinkers. Even though these heavy drinkers would be expected to require more health care, survival bias likely explains this finding, as suggested by previous observation of highest death rates among heavy drinkers (8).

Similarly, the higher use of outpatient services in non-drinkers observed in bivariate analysis disappeared once adjusting for comorbidity, suggesting that poorer health rather than abstinence related to health beliefs was responsible for this association. As shown previously, the non-drinking group is heterogeneous, composed of a mix of never and past drinkers, both subgroups presenting with a poorer health status than current drinkers (8). Consequently to the higher occurrence of chronic conditions and related drug use associated with ageing, older persons have a higher likelihood to stop drinking, the so-called “sick-quitter effect” (10).

## Conclusion

Both the “sick quitter” and “healthy survivor” effects likely explain the lack of significant association between higher intake of alcohol and health services use. More health conscious behavior among low drinkers also likely contributes to this finding.

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**Table 1 : Characteristics of participants and use of health services over 5 years according to alcohol intake**

| | Drinking groups | | | | |
|---|---|---|---|---|---|
| | **Not drinking** | **Light-to-moderate** | **At risk** | **Heavy** | **P-value*** |
| | *N=135* | *N=703* | *N=226* | *N=118* | |
| | 11.4% | 59.5% | 19.1% | 9.9% | |
| **Baseline characteristics** | | | | | |
| Age (mean ± SD) | 67.2 ±1.4 | 67.1 ±1.4 | 66.8 ±1.4 | 66.8 ±1.4 | .007 |
| Men (%) | 18.5 | 40.0 | 50.4 | 59.3 | <.001 |
| Low education (%) † | 70.1 | 62.2 | 66.2 | 66.1 | .275 |
| Comorbidity ($2^+$ chronic diseases, %) | 63.0 | 45.7 | 46.7 | 39.8 | .001 |
| Poor self-rated health (%) | 37.0 | 26.2 | 16.4 | 28.8 | .000 |
| Basic ADL impairment (%)‖ | 17.0 | 8.0 | 5.3 | 11.9 | .001 |
| **Number of physician visits, planned** (mean ± SD) § | **34.0±.32.6** | **27.6±20.8** | **25.9±20.8** | **25.0±23.6** | **.020** |
| Incidence Rate Ratio¶ | **1.23 (1.05-1.44)** | *ref* | 0.94 (0.83-1.05) | 0.91 (0.77-1.06) | |
| Adjusted Incidence Rate Ratio ** | 1.04 (0.90-1.19) | *ref* | 0.99 (0.89-1.10) | 0.92 (0.80-1.05) | |
| **Number of physician visits, unplanned** (mean ± SD) § | 3.5±.3.3 | 2.9±3.8 | 2.6±2.2 | 3.1±5.5 | .419 |
| Incidence Rate Ratio¶ | 1.37 (0.88-2.1) | *ref* | 0.81 (0.58-1.13) | 1.01 (0.62-1.64) | |
| Adjusted Incidence Rate Ratio ** | 1.12 (0.73-1.72) | *ref* | 0.91 (0.66-1.25) | 1.00 (0.63-1.60) | |
| **Number of hospital admissions** (mean ± SD) § | 2.4±1.9 | 2.2±1.6 | 2.1±2.1 | 2.3±0.9 | .848 |
| Incidence Rate Ratio¶ | 1.17 (0.74-1.83) | *ref* | 0.97 (0.68-1.37) | 1.13 (0.69-1.87) | |
| Adjusted Incidence Rate Ratio ** | 0.94 (0.61-1.44) | *ref* | 0.97 (0.69-1.35) | 1.08 (0.67-1.74) | |

* P-value from Chi-square test (categorical variables) or ANOVA (continuous variables)
† Defined as less than 12 years of education (compulsory school or apprenticeship)
‡ Basic Activities of Daily Living were bathing, dressing, using the toilet, transferring, feeding.
§ among participants with at least one physician visit (planned/unplanned) or at least one hospital admission
¶ IRR: Incidence rate ratio from zero-truncated negative binomial regression, including participants with at least one physician visit (planned/unplanned) or at least one hospital admission, respectively
**Adj.IRR: IRR adjusted for all variables in the Table