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Comparison of self-reported measures of alcohol-related dependence among young Swiss men: A study protocol for a cross-sectional controlled sample

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Abstract

Introduction: Short screenings of alcohol-related dependence are needed for population-based assessments. Even if, clinical interviews are reliable diagnosis (often seen as gold standard), it is costly and time consuming and therefore, not suitable for population-based assessments. Therefore, self-reported questionnaires are needed (e.g., alcohol use disorder (AUD) as in the DSM-5) but they may not be reliable. Recent studies called for more evidence-based measurements for population-based screening (e.g., heavy alcohol use over time (HAU)). This study aims to test different self-reported measures of alcohol use (e.g. self-reported AUD and HAU).

Methods and Analysis: Based on stratified random selection, 280 participants will be recruited from the French-speaking subgroup of the Swiss National Science Foundation-supported Cohort Study on Substance Use and Risk Factors (C-SURF) (sample size calculation based on a proportion non-inferiority test with alpha = 5%, a power of 80%, a margin of equivalence of 10%, a difference in sensitivity between self-reported AUD and HAU of 5%, a correlation between AUD and HAU of 0.35, and 15% of dropouts). This cohort is a population-based sample of young Swiss men in their middle 20 (n=2,668). Assessment will include clinical interviews as gold standard of alcohol-related dependence, self-reported alcohol measures (HAU, AUD, and drinking patterns), biomarkers as gold standard of chronic excessive drinking, and health outcomes. To assess the validity of the self-reported alcohol measures, sensitivity analyses will be run. The associations between alcohol-related measures and health outcomes will be tested. And non-response analysis will be run using the previous waves of the C-SURF study using logistic regressions.

Ethics and Dissemination: The study protocol has been approved by the Human Research Ethics Committee of the Canton of Vaud, Switzerland (no. 2017-00776). The results will be

submitted for publication in peer-reviewed journals and presented at national and international conferences.

Trial registration: No health care intervention

Strengths and limitations of this study

Strength: first evaluation of the self-reported outcomes studied compared to a clinical interview, inclusion of a large number of outcomes, available longitudinal data for the participants included in the sample.

Limitations: only men in their middle 20

Background

Substance-related dependence is a major health concern worldwide, with alcohol being described as the substance leading to the most disabling mental disorders (1). Defining and measuring substance-related dependence is difficult and has led to various changes according to social, economic, and political reasons (2). Indeed, substance-related dependence went through several shifts in terminology, definition, and measurement over the last 50 years (2,3). These changes were designed to improve its measure and aimed to be scientifically valid, clinically useful, and understandable by the general public (4). Generally speaking, there is an agreement to define substance-related dependence as a *syndrome of physiological, behavioral, and cognitive phenomena developed after repeated substance use* (5–7). Therefore, "alcohol-related dependence" can be defined as a syndrome of physiological, behavioral, and cognitive phenomena developed after repeated alcohol use. We prefer this term instead of "alcohol dependence," which would be misleading because alcohol

dependence has been used to define a distinct disorder in, for example, in the DSM-IV (7) and ICD-11 and no longer exists in the DSM-5, which combines two disorders, abuse and dependence, into alcohol use disorder (AUD).

Measuring alcohol-related dependence: The gold standard

Assessing alcohol-related dependence needs a clinical interview conducted by an experienced clinician in direct exchange with a patient. Indeed, a clinical interview provides a reliable diagnosis and it is often seen as gold standard. Without an extensive anamnesis, it is difficult to establish a reliable diagnosis because alcohol-related dependence is a syndrome with several physiological, behavioral, cognitive, and psychological processes, and not just "a tick box of symptoms" (8).

Beyond clinical interviews, biochemical investigations are also used to assess chronic excessive drinking (9) without asking people about their alcohol use. Biomarkers do not allow direct testing of the concept of alcohol-related dependence. However, they may be useful to screen for chronic excessive drinking, which may be a strong indicator of alcohol-related dependence. Since they do not rely on self-reports nor judgment of a clinician, they are of great interest in alcohol research. However, clinical diagnoses and biomarker analyses are costly and time consuming and therefore not suitable for general population assessments that are needed for public health planning and monitoring, such as establishing prevalence rates, treatment planning, policy making, and early intervention. Therefore, short quantitative measures of alcohol-related dependence are needed.

Alcohol-related dependence self-reported measures

Several self-reported measures of alcohol-related dependence are already available. In the recent developments of the DSM-5, alcohol-related dependence is measured through 11

criteria designed to diagnose alcohol use disorder (AUD) (10). However, despites the fact that AUD is well defined and that its measure addresses previous issues related to the diagnosis of the DSM-IV (11), several studies reported difficulties related to alcohol-related dependence's measurement using self-reported measures (e.g., 12–14), and a recent study called for more evidence-based measures (2). Thus, there is still a lack of consensus and empirical studies to achieve a reliable self-reported measure of alcohol-related dependence at the population-based level. These self-reported measures do not aim to replace clinical assessments, which are compulsory for diagnostic evaluation and treatment, but would be of great interest for general population screening purposes.

Unfortunately, self-reported questionnaires on alcohol-related dependence such as self-reported questions based on the criteria of AUD (15) may be misinterpreted by respondents and thus are not reliable indicators at the general population level. For example, previous studies highlighted misinterpretation of DSM diagnostic criteria (13,16), contamination by negative thinking patterns of depressive people (17), lack of specificity (14), low positive predictive values (meaning that those who screen positive do not have the disorder) (18), and lack of convergence with clinical diagnoses (5). Young heavy drinkers are especially concerning. They are likely to misinterpret survey questions and to share a misperception of AUD symptoms, such as aftereffects and acute intoxication. Therefore, they are likely to over-report physiological symptoms of withdrawal and tolerance (12). Overall, it seems that self-reports are not always consistent with clinical diagnoses, and clearer/better measures are needed for general population assessment. However, misspecification of self-reported AUD is understudied (12).

Some previous studies suggested that heavy use should be a suitable criterion in future classifications of substance-related dependence (2,19,20). Rehm et al. (2) suggested that alcohol use over time, and more specifically heavy alcohol use (HAU) over time, is

responsible for the physiological changes, symptoms, social consequences, and burden of disease associated with the current definition of alcohol-related dependence. They concluded that HAU should be the relevant indicator of alcohol-related dependence. Moreover, the use of HAU also may diminish stigmatization associated with alcohol-related dependence (5,19,21,22) since alcohol use over time is less stigmatized than AUD. However, there are at least two important issues. The first one is the lack of definition of HAU: how many drinks are needed to defined "heavy use," and how many months are needed to define "over time"? Currently, some indicators of alcohol use over time are available; for example, two drinks per day maximum is defined as low-risk alcohol consumption (23). Second, some studies reported that HAU is not a sufficient indicator of addictive behavior (24), but empirical studies investigating this question using reliable measures of alcohol-related dependence have not been conducted.

An alternative operationalization of alcohol-related dependence has recently been suggested. Martin, Langenbucher, Chung and Sher (25) proposed that substance use disorders should focus on what they called 'core' features (i.e., primary symptoms indexing internal dysfunctions) and not on 'ancillary' features (i.e., consequences). According to these authors, consequences should not be used to measure substance-related dependence because they are context-dependent, manifoldly determined, and not necessarily related to one substance but to multiple substances. It is well established that AUD is associated with several detrimental consequences as consequences are part of the DSM-5 definition. However, non-disordered AUD can also result in consequences (14). Therefore, Martin et al. (25) suggested assessing alcohol-related dependence with primary symptoms and removing consequences from its measure in order to get a more reliable measure; for example, to decrease the number of false negatives. To our knowledge, no empirical study tested this proposition, and data are thus needed.

Aim of the study

Based on clinical interviews designed to diagnose alcohol-related dependence, the main aim of this study is to test the quality of self-reported AUD to assess alcohol-related dependence in the general population. Another aim of this study is to test whether self-reported HAU can be used instead of self-reported AUD as a measure of alcohol-related dependence in a general population-based sample, using a quantitative approach. It will also test whether self-reported AUD focusing on primary symptoms and excluding alcohol-related consequences is a better assessment of alcohol-related dependence than self-reported AUD in its traditional definition.

Methods/Design

Study design

The study is a single center, national, controlled study with a stratified random sample selection and a cross-sectional design.

Setting

The study will be conducted in the Lausanne University Hospital (CHUV) in the Alcohol Treatment Centre. This facility is an urban public hospital serving 770,000 people. It is one of the five teaching university hospitals located in Switzerland.

Population and sample

Population

Our study is a large nested project of the ongoing longitudinal C-SURF study (26) supported by the Swiss National Foundation (SNF grant 33CSC0_122679, 33CSC0_139467, and 33CS30_148493). The C-SURF study is representative of young men around 20 years old. Young men are the study focus because they are a high-risk population regarding alcohol use (27). In collaboration with the C-SURF study, participation in the present project will be proposed to all French-speaking participants who were recruited within the Lausanne army recruitment center and who answer the second follow-up of C-SURF in the following six months with a valid email address (n = 2,668). French-speakers are the targets of this study because C-SURF covered all French speakers, whereas the German-speaking part uses only a subgroup of all German-speaking Swiss men. To focus on French speakers also reduces costs by using only one language for clinical assessment and a narrower area from which people have to travel for the clinical interviews. In addition, C-SURF collected extensive data, and therefore additional detailed information about participants for the present project will be available. C-SURF also provides an up-to-date address registry and a tracking team, which will be useful to keep dropout rates low.

Recruitment

First, all French-speaking men involved in the C-SURF study on September 25, 2017 with a valid email adress have been invited by email to complete a ten-question online version of the Alcohol Use Disorder Identification Test (AUDIT) (5 min) (28, 29) and have been informed that they may be contacted for the whole study if they are selected within the following six months. A second email was sent two weeks later to the participants who did not answer the questionnaire.

Second, we will select participants using a random stratified sample selection. All the participants who complete the AUDIT and meet the inclusion criteria (see below) will be separated in two strata (AUDIT $\geq$ 13; AUDIT < 13), called groups hereafter. A total of 173

participants will be selected in the first group and 107 in the second group (using randomized numbers with the software R).

Selected participants will be contacted by phone by the psychologists to invite them to participate in the clinical assessment. An appointment at the CHUV will be scheduled if a participant agrees to participate.

Procedure

During assessment in the CHUV, participants will complete a computer-assisted questionnaire. Then, they will participate in the structured interview with a psychologist. Biological samples will be collected afterwards. The visit will take 90 minutes on average. The participants will be blinded to the group to which they belong. The interviewers will also be blinded to the participants' group. The participant will be given an oral feedback on their alcohol consumption after the interview and a written feedback at the end of the study.

Inclusion/exclusion criteria

This study is nested in the C-SURF study, of which the inclusion criteria were:

- All young Swiss men at the army recruitment centers of Lausanne, Windisch and Mels.
- All French-speaking cantons of Switzerland are included.

Within the French-speaking participants of the C-SURF, participants of the present study will be eligible if:

- They have a valid email address.
- They completed the AUDIT.
- They are randomly selected for the study's participation.

The exclusion criteria of our study are the following:

- They do not provide an informed consent to participate in the study.

- They have a score of zero on the three first questions of the AUDIT questionnaire related to alcohol use during the previous 12 months.

[Figure 1 about here]

Hypotheses and research questions

Primary outcomes

Hypothesis 1. Self-reported AUD is not a reliable measure of alcohol-related dependence.

Hypothesis 2. HAU is a reliable measure of alcohol-related dependence.

Secondary outcomes

We also aim to investigate important secondary questions related to AUD and drinking patterns, as follows.

Research question 1. This question is related to the pattern of alcohol use and its relationship with alcohol-related dependence. Risky single-occasion drinkers, drinkers who drink six or more drinks on a single occasion, are more likely to be classified with alcohol-related dependence than non-risky single-occasion drinkers. We hypothesize that for the same moderate level of alcohol use, risky single-occasion drinking (RSOD) will be associated with a higher level of alcohol-related dependence, since this drinking pattern has been described as harmful (29–32). For example, people who drink seven drinks on Friday and Saturday (total 14 drinks per week) will have a higher level of alcohol dependence than people who drink three drinks on four different days (total 14 drinks per week). This hypothesis applies for moderate drinking levels because those who drink heavily are probably risky single-occasion drinkers (e.g., five drinks per day). We also hypothesize that RSOD will also be associated with increased self-reported AUD (33).

Research question 2. The second question deals with cut-offs for the biomarkers of chronic excessive drinking. More investigations are needed in order to propose relevant cut-offs for EtG (Ethylglucuronide) in hair and PEth (Phosphatidylethanol) in blood. Evidence is still needed to define unhealthy alcohol use for decision making. We will test the diagnostic performance of EtG and PEth compared to the clinical interviews. We will also test whether EtG and PEth are potential measures of RSOD, which is a question that has not been yet at focus, even if RSOD is a common drinking pattern among young people.

Research question 3. Another transversal research question will be to investigate non-response bias. Non-response bias is a crucial issue in surveys focusing on substance use. Indeed, contrariwise to most of the studies in which information about non-respondents are generally unavailable, data about the population (i.e., C-SURF participants) will be available (e.g. self-reported alcohol use, AUD, alcohol-related consequences, non-alcohol-related consequences, and mental and physical health). Therefore, we will be able to estimate non-response bias and predictors of non-response among participants who will be contacted to participate in the present study.

Endpoint

Primary endpoints

1. *Alcohol-related dependence.* Alcohol-related dependence will be assessed using clinical interviews over a 12 months period. This diagnosis, our gold standard, will be based on the Diagnostic Interview for Genetic Studies (DIGS, 33). It enables a comprehensive assessment of alcohol-related dependence and generates reliable diagnoses. It allows for the assessment of a comprehensive psychiatric diagnosis of alcohol-related dependence based on DSM-5 criteria. Its semi-structured format ensures homogeneity across patients and interviewers. We will add three questions related to craving. Craving was added in the DSM-5, and the DIGS is

available only according to the DMS-IV definition of alcohol-related dependence. Three questions from the questionnaire, "Obsessive Compulsive Drinking Scale," will be tested and added to propose a DSM-5 version of the DIGS (35).

2. *Alcohol use disorder*. We will measure AUD as defined in the DSM-5, with 11 criteria (10). We will use the cut-offs recommended in the DSM-5 to define presence or absence of AUD (i.e., two criteria out of 11 criteria), and also a continuous scale of criteria (from zero to 11, with a sum score of the 11 criteria). Moreover, following Martin et al. (25), a restricted definition of primary symptoms of AUD will be computed by summing the items related to internal dysfunction (6 criteria). We will use a continuous scale of criteria, since no cut-off is available for this operationalization.

3. *Alcohol use over time.* Alcohol use over time will be measured with an extended quantity-frequency (QF) questionnaire. The extended QF questionnaire captures the variability in drinking habits better than with other instruments (36), providing separate information on weekends and weekdays over a period of time (12 months in our study). The measures are converted into a total number of drinks per week by multiplying average frequency of drinking and quantity of drinking. In order to define HAU, we will test different cut-offs (e.g., the traditional cut-offs of two and four drinks on average per day and empirical cut-offs).

4. *Number of drinks according to past-week diary.* The number of drinks during the past week assessed for each day separately will be added to create a total number of drinks for the whole week. A short-term recall measure (7-day diary) will ask for the number of drinks during the past week on each day separately. This measure allows testing whether participants drink every day and how many drinks per day they drink.

5. *Retrospective alcohol use.* We will also collect more information on alcohol use over time using retrospective questions for participants at age 10-15, 20 and 25 using questions used in the European Investigation into Cancer and Nutrition (EPIC) study, which described the

trends of self-reported past consumption of alcohol use (37). Retrospective alcohol use will be modified to create an average number of drinks per week at age 10-15, 20, and 25. This measure will provide information on alcohol use over time.

6. *Biomarkers of chronic excessive drinking.* We will use the EtG in hair and the PEth in whole capillary blood. Two locks of hair (alternatively arm/chest hair) will be collected to assess EtG, and a capillary blood sample on a dried blood spot will be taken to measure PEth. Both biomarkers will be analyzed by liquid chromatography coupled to tandem mass spectrometry using ISO-validated methods. EtG and PEth are two recent biomarkers that appear especially reliable (9,38,39), whereas traditional biomarkers (carbohydrate-deficient transferring and gamma-glutamyl-transferase) lack sensitivity and/or specificity, especially among young people showing a typical RSOD behavior on weekends or special occasions. Hair EtG is efficient to detect alcohol abuse and cut-offs have been proposed for at-risk drinkers (> 20/30 g of ethanol/day) and heavy drinkers (> 60 g of ethanol/day). Its sensitivity and specificity are very high (> 95%). On the contrary, it is less reliable for low levels of alcohol use. By contrast, PEth is useful to detect low levels of alcohol use during the last two to four weeks. Indeed, PEth has demonstrated a very high specificity (theoretically 100%).

Secondary endpoints

1. *Risky single-occasion drinking*. RSOD is often measured with an ordinal scale (e.g. "*no RSOD*," "*less than monthly RSOD*," "*monthly RSOD*," "*weekly RSOD*," and "*daily RSOD*") and with a cut-off of five or six drinks on a single occasion (40). The current study will propose more precise operationalization of RSOD (e.g., number of drinks per occasion, duration of each occasion, and continuous scale for number of occasions).

2. *Health issues and illnesses*. The Short Form Health Survey (SF-12, 40) will be included with its two subscales: the mental component summary (mental and social health), and physical component summary (physical health).

3. *Consequences*. Sixteen consequences already used in C-SURF, which are not explicitly substance-related (42), will be selected from standard instruments (43–46). Two sum-scores of consequence-associated scores will be computed: the first for social consequences and the second for health consequences. In addition, alcohol-related consequences will be assessed as in the DSM-5 (10).

4. *Quality of life*. The World Health Organization Quality of Life Instrument (WHOQoL-BREF) has been validated widely, and it was found to be reliable and valid for use among patients with alcohol-related dependence (47). There are 26 questions rated on a five-point scale composed by two general question of quality of life and four dimensions: physical health (seven items), psychological health (six items), social relationships (three items) and environment (8 items). Each question was rated in reference to the last two weeks. A percentage rating within each domain is computed with scores ranging from zero (lowest QOL) to 100 (highest QOL).

5. *Life satisfaction*. The Satisfaction With Life Scale (SWLS) will be use to assess life satisfaction (48). A mean score of the five questions of the SWLS will be computed.

Other variables

For the selection of participants, we will use the AUDIT (27,28). The AUDIT is a ten-item screening measure for AUD (49,50) developed by the World Health Organization, which includes three questions on dependence, four questions on specific consequences of harmful alcohol use, and three questions on hazardous alcohol use. It has been described as a reliable screening tool of AUD (51).

We will also assess demographic variables: age, educational status, and professional status.

Based on the C-SURF data (three waves already collected and available), we will match information on demographics, health, and substance use.

Ethical aspects and safety

Consent and risks

All procedures performed in studies involving human participants will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol, information letters, questionnaires, and the informed consent forms of the study have been approved by the Human Research Ethics Committee of the Canton of Vaud, Switzerland (no. 2017-00776). There is no expected adverse event or side effect for participants. Informed consent will be obtained from all individual participants included in the study.

Confidentiality of the data

Data generation, transmission, storage, and analysis of health-related personal data and the storage of biological samples within this project will strictly follow the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5. Data protection and confidentiality will be guaranteed.

Patient and Public Involvement

Patients and public were not involved.

Statistical analysis

Sample size

There is no available information about the psychometric properties of the self-reported AUD nor of HAU. Therefore, it was not possible to estimate a precise sample size in a power

calculation. To ensure that we have enough alcohol-related dependent participants to test the hypothesis of HAU being equivalent or better than self-reported AUD, we made several sample size calculations based on different scenarios of possible sensitivity of self-reported AUD (sensitivity between 0.2 and 0.8) using a proportion non-inferiority test with alpha = 5%, a margin of equivalence of 10%, and a difference in sensitivity between self-reported AUD and HAU of 5% (52). The worst scenario is for sensitivity around 50% and no correlation between self-reported AUD and HAU. In this worst scenario, for a power of 80%, 135 alcohol-related dependent participants are needed (as shown in Figure 2). In a favorable scenario, with a power of 80% and a middle/large correlation (supported by the C-SURF data: r = 0.50), a total of 67 participants with alcohol-related dependence are needed. We decided to choose a scenario between the worst and the most favorable with a correlation between self-reported AUD and HAU of 0.35, which is a moderate correlation between two related but different concepts. In this scenario, 86 participants with alcohol-related dependence are needed. Therefore, we will select at least 86 participants with alcohol-related dependence and 86 participants without alcohol-related dependence.

[Figure 2 about here]

The AUDIT score will be used to select participants. Alcohol-related dependence is defined with a cut-off of 13 at AUDIT (53), with a sensitivity ranging between 0.78 and 0.90 and a specificity ranging between 0.87 and 0.92 (51,53). The positive predictive values were estimated between 0.40 and 0.88 (51,53). Thus, by randomly selecting 151 participants with AUDIT greater or equal to 13 and a positive predicted value of 0.64 (mid-point between 0.40 and 0.88), there is a 95% probability of selecting at least 86 participants who are true positive. The negative predictive values were estimated at 0.97 (51,53). Therefore, we will select 93 participants with AUDIT lower than 13 in order to have a 95% probability of selecting at least 86 true negative non-alcohol dependent participants. The psychologists will be blinded to the

participants' AUDIT scores. In order to avoid issues related to attrition, we added 15% of participants in each group, a total of 173 participants with AUDIT ≥ 13 and 107 participants with AUDIT < 13 will be invited in each group (N= 280).

Data Analyses

Analyses 1 (primary outcomes): HAU and AUD as measures of alcohol-related dependence

Considering the clinical interviews as a gold standard of alcohol-related dependence, and biomarkers as a gold standard of chronic excessive drinking, we will test the diagnostic performance of self-reported AUD and HAU measures to see whether they are suitable ways to assess alcohol-related dependence. We will use effect sizes to compare the correlations (R^2 to test common variance between measures and clinical effect size), and we will use Fisher's R to Z transformations to compare whether the correlations are significantly different from one another. Then, we will use dichotomized variables and test sensitivity, specificity, positive predicted value, and negative predicted value using the receiver operating characteristic (ROC) curves. To dichotomize alcohol use, different theory-oriented cut-offs will be compared (four, two, and one drink(s) per day), and data-driven models will also be tested using stratum specific likelihood ratio analysis.

Analyses 2 (primary and secondary outcomes): Associations with health outcomes and alcohol-related variables

We will compare outcomes' associations with the gold standards and the different self-reported measures (HAU, self-reported AUD, and self-reported AUD without consequences). Effect sizes will be compared in order to know which measure is the best predictor of health and psychosocial issues and which one most resembles the associations with the gold standards.

Analyses 3 (secondary research question): Association of RSOD with alcohol-related dependence

Associations of RSOD with the gold standard of alcohol-related dependence will be performed, adjusting for alcohol use (extended QF questionnaire) to assess its independent effect, and including an interaction between alcohol use and RSOD to investigate their combined effect.

Analyses 4 (secondary research question): Cut-off for biomarkers and associations with RSOD

The diagnostic performance of EtG and PEth will be calculated for their optimal cut-off values selected with the ROC curves. Comparisons with clinical interviews, and HAU will be performed. We will also test whether EtG and PEth are potential measures of RSOD, using EtG and PEth cut-offs to predict RSOD using correlations and ROC curves. Different cut-offs will be tested in these analyses.

Analyses 5 (secondary research question): Non-response bias

We will compare non-respondents to respondents using the information available in the previous waves of the C-SURF study using logistic regressions.

All analyses will use a two-sided $\alpha = 0.05$. Statistical software will include SPSS, Stata, and R.

Discussion

The main aim of this study is to test the quality of the self-reported AUD (also focusing on primary symptoms and excluding alcohol-related consequences) and of the self-reported HAU as measures of alcohol-related dependence as defined by the DSM-5 in a general population.

The psychometric properties of the self-reported AUD and of the HAU will be tested against clinical interviews designed to diagnose alcohol-related dependence.

From an international perspective, the proposed project aims to address some methodological issues highlighted in recent studies related to the measure of substance-related dependence, and more specifically, alcohol-related dependence. The project will provide evidence regarding two important issues. First, it will test whether self-reported AUD, which is extensively used in alcohol research, is a reliable way to assess alcohol-related dependence. Second, it will investigate whether HAU is a reliable measure of alcohol-related dependence. Therefore, the study will provide insights on its capacity to capture alcohol-related dependence. The results of the study may have a large impact on future research on alcohol. It will suggest a better way to assess alcohol-related dependence in population-based samples and for screening perspectives. Additionally, the project will investigate thresholds needed for decision making (early intervention and treatment), test the effect of drinking patterns on self-reported AUD, and determine cut-offs for biomarkers. These cut-offs will be useful for legal medicine, which needs further studies for decision making regarding alcohol abstinence.

From a national perspective, this study will provide a valid prevalence rate of alcohol-related dependence among French-speaking young Swiss men in their middle-20s. It will be useful from a public health point of view. Moreover, cut-offs for unhealthy alcohol use will be proposed, which may be relevant for preventive purposes and may identify at-risk youths in Switzerland. It will improve screening for unhealthy alcohol use. It would also be useful for general practitioners to detect alcohol-related dependent persons (54).

The current study is designed to provide evidence regarding the assessment of alcohol-related dependence in the general population and especially among young people. Potential benefits to society include a better understanding and evaluation of alcohol-related dependence, improvements of practices, and future development of adequate public health planning. It will

help to identify at-risk persons and groups. It may change the practices from a clinical and public health perspective, such as the use of alternative measures to screen for alcohol-related dependence and identify at-risk alcohol users, and from a research perspective, for example to stop using unreliable self-reported addiction scales and thus to provide strong support to future findings in alcohol research.

List of abbreviations

AUD: Alcohol use disorder

AUDIT: Alcohol Use Disorder Identification Test

CHUV: Lausanne University Hospital ("**C**entre **H**ospitalier **U**niversitaire **V**audois")

C-SURF: Cohort Study of Substance Use and Risk Factors

DIGS: Diagnostic Interview for Genetic Studies

DSM: Diagnostic and Statistical Manual of Mental Disorders

EPIC: European Investigation into Cancer and Nutrition

EtG: Ethylglucuronide

HAU: Heavy alcohol use

PEth: Phosphatidylethanol

QF: Quantity-frequency

QOL: Quality of life

RSOD: Risky single-occasion drinking

SF-12: Short Form Health Survey

SNF: Swiss National Foundation

ROC: Receiver operating characteristic

SWLS: Satisfaction With Life Scale

WHOQOL: World Health Organization Quality of Life

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol, information letters, questionnaires, and the informed consent forms of the study have been approved by the Human Research Ethics Committee of the Canton of Vaud, Switzerland (no. 2017-00776). There is no expected adverse event or side effect for participants. Informed consent will be obtained from all individual participants included in the study.

Consent for publication

Not applicable

Availability of data and material

'Not applicable'

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

KI and SB wrote the manuscript. All authors critically reviewed the manuscript for important intellectual content. The study design and research proposal were mainly developed by SB and KI. GG, FS, and JBD made substantial contributions to the conception and the design of

the study. The intervention was developed by SB and KI. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the final manuscript.

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Figure legends

Figure 1 legend: C-SURF: *Cohort Study of Substance Use and Risk Factors****; AUDIT:*** *Alcohol Use Disorder Identification Test.*

Figure 2 legend: AUD sens: *Alcohol use disorder sensitivity;* ***HAU sens:*** *Heavy alcohol use sensitivity; cor: correlation.*

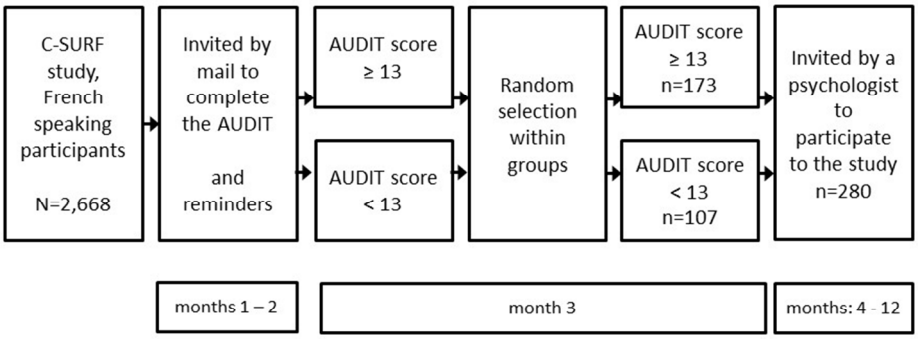

Figure 1 legend: C-SURF: Cohort Study of Substance Use and Risk Factors; AUDIT: Alcohol Use Disorder Identification Test.

254x190mm (96 x 96 DPI)

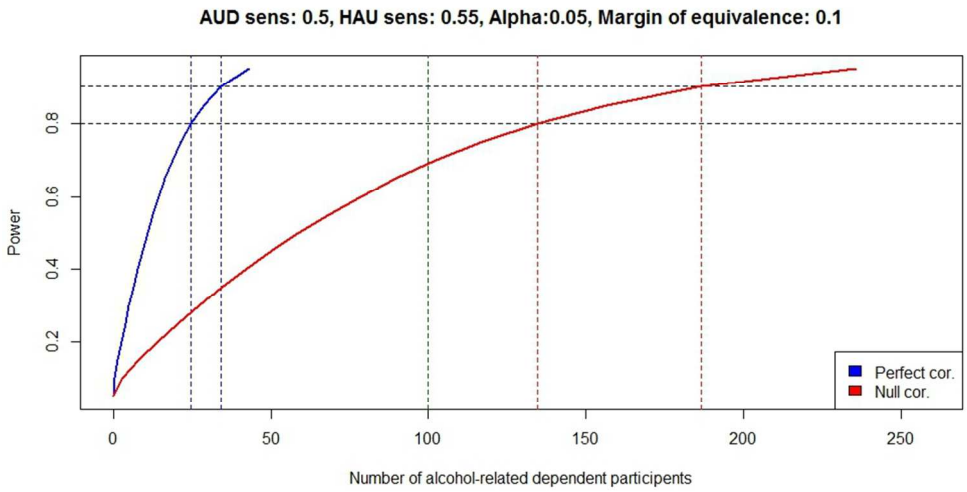

Figure 2 legend: AUD sens: Alcohol use disorder sensitivity; HAU sens: Heavy alcohol use sensitivity; cor: correlation.

351x186mm (72 x 72 DPI)

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Comparison of self-reported measures of alcohol-related dependence among young Swiss men: A study protocol for a cross-sectional controlled sample

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Comparison of self-reported measures of alcohol-related dependence among young Swiss men: A study protocol for a cross-sectional controlled sample

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Abstract

Introduction: Short screenings of alcohol-related dependence are needed for population-based assessments. A clinical interview constitutes a reliable diagnosis often seen as gold standard, but it is costly and time consuming and as such, not suitable for population-based assessments. Therefore, self-reported questionnaires are needed (e.g., alcohol use disorder (AUD) as in the DSM-5) but their reliability is questionable. Recent studies called for more evidence-based measurements for population-based screening (e.g., heavy alcohol use over time (HAU)). This study aims to test the reliability of different self-reported measures of alcohol use.

Methods and Analysis: Based on stratified random selection, 280 participants will be recruited from the French-speaking subgroup of the Swiss National Science Foundation-supported Cohort Study on Substance Use and Risk Factors (C-SURF). This cohort is a population-based sample of young Swiss men in their middle 20 (n=2,668). The sample size calculation is based on a proportion non-inferiority test (alpha=5%, power=80%, margin of equivalence=10%, difference in sensitivity between self-reported AUD and HAU=5%, correlation between AUD and HAU=0.35, and dropouts=15%). Assessment will include a clinical interview as the gold standard of alcohol-related dependence, self-reported alcohol measures (HAU, AUD, and drinking patterns), biomarkers as gold standards of chronic excessive drinking, and health outcomes. To assess the validity of the self-reported alcohol measures, sensitivity analyses will be run. The associations between alcohol-related measures and health outcomes will be tested. An non-response analysis will be run using the previous waves of the C-SURF study using logistic regressions.

Ethics and Dissemination: The study protocol has been approved by the Human Research Ethics Committee of the Canton of Vaud, Switzerland (no. 2017-00776). The results will be

submitted for publication in peer-reviewed journals and presented at national and international conferences.

Trial registration: No health care intervention

Strengths and limitations of this study

Strengths:

- Evaluation of self-reported outcomes compared to a clinical interview based on the DSM-5
- Inclusion of a large number of outcomes: clinical interview, biological material, and self-reported measures
- Nested project in a longitudinal study: longitudinal data available for the participants included in the sample, non-response analysis.

Limitations:

- Only men in their middle 20s
- The available data to test reliability of the self-reported measures are separated by one year

Background

Substance-related dependence is a major health concern worldwide, with alcohol being described as the substance leading to the most disabling mental disorders (1). Defining and measuring substance-related dependence is difficult and has led to various changes according to social, economic, and political reasons (2). Indeed, substance-related dependence went through several shifts in terminology, definition, and measurement over the last 50 years (2,3). These changes were designed to improve its measure and aimed to be scientifically valid, clinically useful, and understandable by the general public (4). Generally speaking, there is an agreement to define substance-related dependence as a *syndrome of physiological, behavioral, and cognitive phenomena developed after repeated substance use* (5–7). Therefore, "alcohol-related dependence" can be defined as a syndrome of physiological, behavioral, and cognitive phenomena developed after repeated alcohol use. We prefer this term instead of "alcohol dependence," which would be misleading because alcohol dependence has been used to define a distinct disorder in, for example, in the DSM-IV (7) and ICD-11 and no longer exists in the DSM-5, which combines two disorders, abuse and dependence, into alcohol use disorder (AUD).

Measuring alcohol-related dependence: the gold standard

Assessing alcohol-related dependence requires a clinical interview conducted by an experienced clinician in direct exchange with a patient. Indeed, a clinical interview provides a reliable diagnosis and it is often seen as gold standard. Without an extensive anamnesis, it is difficult to establish a reliable diagnosis because alcohol-related dependence is a syndrome with several physiological, behavioral, cognitive, and psychological processes, and not just "a tick box of symptoms" (8).

Beyond clinical interviews, biochemical investigations are also used to assess chronic excessive drinking (9) without asking people about their alcohol use. Biomarkers do not allow direct testing of the concept of alcohol-related dependence. However, they may be useful to screen for chronic excessive drinking, which may be a strong indicator of alcohol-related dependence. Since they do not rely on self-reports nor judgments of a clinician, they are of great interest in alcohol research.

However, clinical diagnoses and biomarker analyses are costly and time consuming and therefore not suitable for general population assessments that are needed for public health planning and monitoring, such as establishing prevalence rates, treatment planning, policy making, and early intervention. Therefore, short quantitative measures of alcohol-related dependence are needed.

Alcohol-related dependence self-reported measures

Several self-reported measures of alcohol-related dependence are already available. In the recent developments of the DSM-5, alcohol-related dependence is measured through eleven criteria designed to diagnose alcohol use disorder (10). However, despites the fact that AUD is well defined and that its measure addresses previous issues related to the diagnosis of the DSM-IV (11), several studies reported difficulties related to alcohol-related dependence's measurement using self-reported measures (e.g., 12–14). For example, the self-reported questions based on the criteria of AUD (10) may be misinterpreted by respondents. Previous studies highlighted misinterpretation of DSM diagnostic criteria (13,15), contamination by negative thinking patterns of depressive people (16), lack of specificity (14), low positive predictive values (meaning that those who screen positive do not have the disorder) (17), and lack of convergence with clinical diagnoses (5). Young heavy drinkers are especially concerned. They are likely to misinterpret survey questions and to share a misperception of

AUD symptoms, such as aftereffects and acute intoxication. Therefore, they are likely to over-report physiological symptoms of withdrawal and tolerance (12). Moreover, it seems that self-reports are not always consistent with clinical diagnoses. However, misspecification of self-reported AUD is understudied (12).

As a consequence of these pitfalls, a recent study called for more evidence-based measures (2). Some previous studies proposed heavy use as a suitable criterion in future classifications of substance-related dependence (2,18,19). Rehm et al. (2) suggested that alcohol use over time, and more specifically heavy alcohol use (HAU) over time, is responsible for the physiological changes, symptoms, social consequences, and burden of disease associated with the current definition of alcohol-related dependence. They concluded that HAU should be a relevant indicator of alcohol-related dependence. Moreover, the use of HAU also may diminish stigmatization associated with alcohol-related dependence (5,18,20,21) since alcohol use over time is less stigmatized than AUD. However, there are at least two important issues. The first one is the lack of definition of HAU: how many drinks are needed to defined "heavy use," and how many months are needed to define "over time"? Currently, some indicators of alcohol use over time are available; for example, two drinks per day maximum is defined as low-risk alcohol consumption (22). Second, some studies reported that HAU is not a sufficient indicator of addictive behavior (23), but empirical studies investigating this question using reliable measures of alcohol-related dependence have not been conducted. This measure does not aim to replace clinical assessments, which are compulsory for diagnostic evaluation and treatment, but would be of great interest for general population screening purposes. Thus, there is still a lack of consensus on which measure should be used and of empirical studies designed to test its reliability.

An alternative operationalization of alcohol-related dependence has recently been suggested. Martin, Langenbucher, Chung and Sher (24) proposed that substance use disorders should

focus on what they called 'core' features (i.e., primary symptoms indexing internal dysfunctions) and not on 'ancillary' features (i.e., consequences). According to these authors, consequences should not be used to measure substance-related dependence because they are context-dependent, manifoldly determined, and not necessarily related to one substance but to multiple substances. It is well established that AUD is associated with several detrimental consequences as consequences are part of the DSM-5 definition. However, non-disordered AUD can also result in consequences (14). Therefore, Martin et al. (24) suggested assessing alcohol-related dependence with primary symptoms and removing consequences from its measure in order to get a more reliable measure; for example, to decrease the number of false negatives. To our knowledge, no empirical study tested this proposition, and data are thus needed.

Aim of the study

Based on clinical interviews designed to diagnose alcohol-related dependence, the main aim of this study is to test the quality of self-reported AUD to assess alcohol-related dependence in the general population. Another aim of this study is to test whether self-reported HAU can be used instead of self-reported AUD as a measure of alcohol-related dependence in a general population-based sample. It will also test whether self-reported AUD focusing on primary symptoms and excluding alcohol-related consequences is a better assessment of alcohol-related dependence than self-reported AUD in its traditional definition.

Methods/Design

Study design

The study is a single centre, national, controlled study with a stratified random sample selection and a cross-sectional design.

Setting

The study will be conducted in the Lausanne University Hospital (CHUV) in the Alcohol Treatment Centre. This facility is an urban public hospital serving 770,000 people. It is one of the five teaching university hospitals located in Switzerland.

Population and sample

Population

Our study is a large nested project of the ongoing longitudinal C-SURF study supported by the Swiss National Foundation (SNF grant 33CSC0_122679, 33CSC0_139467, and 33CS30_148493) (25). The C-SURF study is representative of young men around 20 years old. Young men are the study focus because they are a high-risk population regarding alcohol use (26). In collaboration with the C-SURF study, participation in the present project will be proposed to all French-speaking participants who were recruited within the Lausanne army recruitment center and who answer the second follow-up of C-SURF in the following six months with a valid email address (n=2,668). French-speakers are the targets of this study because C-SURF covered all French speakers, whereas the German-speaking part uses only a subgroup of all German-speaking Swiss men. To focus on French speakers also reduces costs by using only one language for clinical assessment and a narrower area from which people have to travel for the clinical interview. In addition, C-SURF collected extensive data, and therefore additional detailed information about participants for the present project will be

available. C-SURF also provides an up-to-date address registry and a tracking team, which will be useful to keep dropout rates low.

Recruitment

First, all French-speaking men involved in the C-SURF study on September 25, 2017 with a valid email adress have been invited by email to complete a ten-question online version of the Alcohol Use Disorder Identification Test (AUDIT) (five minutes) (27, 28) and have been informed that they may be contacted for the whole study if they are selected within the following six months. A second email was sent two weeks later to the participants who did not answer the questionnaire.

Second, we will select participants using a random stratified sample selection. All the participants who complete the AUDIT and meet the inclusion criteria (see below) will be separated in two strata (AUDIT≥13; AUDIT<13), called groups hereafter. A total of 173 participants will be selected in the first group and 107 in the second group, using randomized numbers with the software R.

Selected participants will be contacted by phone by the psychologists to invite them to participate in the clinical assessment. An appointment at the CHUV will be scheduled if a participant agrees to participate. The whole procedure of recruitment is presented in Figure 1.

Procedure

During assessment in the CHUV, participants will complete a computer-assisted questionnaire. Then, they will participate in the structured interview with a psychologist. Biological samples will be collected afterwards. The visit will take 90 minutes on average. The participants will be blinded to the group to which they belong. The interviewers will also be blinded to the participants' group. The participant will be given an oral feedback on their alcohol use after the interview and a written feedback at the end of the study.

Inclusion/exclusion criteria

This study is nested in the C-SURF study, of which the inclusion criteria were:

- All young Swiss men at the army recruitment centre of Lausanne;
- All French-speaking cantons of Switzerland are included.

Within the French-speaking participants of the C-SURF, participants of the present study will be eligible if:

- They have a valid email address;
- They completed the AUDIT;
- They are randomly selected for the study's participation.

The exclusion criteria of our study are the following:

- They do not provide an informed consent to participate in the study;
- They have a score of zero on the three first questions of the AUDIT questionnaire related to alcohol use during the previous 12 months.

[Figure 1 about here]

Hypotheses and research questions

Primary outcomes

Hypothesis 1. Self-reported AUD is not a reliable measure of alcohol-related dependence.

Hypothesis 2. HAU is a reliable measure of alcohol-related dependence.

Secondary outcomes

We also aim to investigate important secondary questions related to AUD and drinking patterns, as follows.

Research question 1. This question is related to the pattern of alcohol use and its relationship with alcohol-related dependence. Risky single-occasion drinkers, drinkers who drink six or

more drinks on a single occasion, are more likely to be classified with alcohol-related dependence than non-risky single-occasion drinkers. We hypothesize that for the same moderate level of alcohol use, risky single-occasion drinking (RSOD) will be associated with a higher level of alcohol-related dependence, since this drinking pattern has been described as harmful (28–31). For example, people who drink seven drinks on Friday and Saturday (total 14 drinks per week) will have a higher level of alcohol dependence than people who drink three drinks on four different days (total 14 drinks per week). This hypothesis applies for moderate drinking levels because those who drink heavily are probably risky single-occasion drinkers (e.g., five drinks per day). We also hypothesize that RSOD will also be associated with increased self-reported AUD (32).

Research question 2. The second question deals with cut-offs for the biomarkers of chronic excessive drinking. More investigations are needed in order to propose relevant cut-offs for EtG (Ethylglucuronide) in hair and PEth (Phosphatidylethanol) in blood. Evidence is still needed to define unhealthy alcohol use for decision making. We will test the diagnostic performance of EtG and PEth compared to the clinical interviews. We will also test whether EtG and PEth are potential measures of RSOD, which is a question that has not been yet at focus, even if RSOD is a common drinking pattern among young people.

Research question 3. Another transversal research question will be to investigate non-response bias. Non-response bias is a crucial issue in surveys focusing on substance use. Indeed, contrariwise to most of the studies in which information about non-respondents are generally unavailable, data about the population (i.e., C-SURF participants) will be available (e.g. self-reported alcohol use, AUD, alcohol-related consequences, non-alcohol-related consequences, and mental and physical health). Therefore, we will be able to estimate non-response bias and predictors of non-response among participants who will be contacted to participate in the present study.

Endpoint

Primary endpoints

1. *Alcohol-related dependence.* Alcohol-related dependence will be assessed using a clinical interview over a 12 months period. This diagnosis, our gold standard, will be based on the Diagnostic Interview for Genetic Studies (DIGS, 33). It enables a comprehensive assessment of alcohol-related dependence and generates reliable diagnoses. It allows for the assessment of a comprehensive psychiatric diagnosis of alcohol-related dependence based on DSM-5 criteria. Its semi-structured format ensures homogeneity across patients and interviewers. We will add three questions related to craving (34). Craving was added in the DSM-5, and the DIGS is available only according to the DMS-IV definition of alcohol-related dependence.

2. *Alcohol use disorder*. We will measure AUD as defined in the DSM-5, with 11 criteria (10). We will use the cut-offs recommended in the DSM-5 to define presence or absence of AUD (i.e., two criteria out of 11 criteria), and also a continuous scale of criteria (from zero to 11, with a sum score of the 11 criteria). Moreover, following Martin et al. (24), a restricted definition of primary symptoms of AUD will be computed by summing the items related to internal dysfunction (6 criteria). We will use a continuous scale of criteria, since no cut-off is available for this operationalization.

3. *Alcohol use over time.* Alcohol use over time will be measured with an extended quantity-frequency (QF) questionnaire. The extended QF questionnaire captures the variability in drinking habits better than with other instruments (35), providing separate information on weekends and weekdays over a period of time (12 months in our study). The measures are converted into a total number of drinks per week by multiplying average frequency of drinking and quantity of drinking. In order to define HAU, we will test different cut-offs (e.g., the traditional cut-offs of two and four drinks on average per day and empirical cut-offs).

4. *Number of drinks according to past-week diary.* The number of drinks during the past week assessed for each day separately will be added to create a total number of drinks for the whole week. A short-term recall measure (7-day diary) will ask for the number of drinks during the past week on each day separately. This measure allows testing whether participants drink every day and how many drinks per day they drink.

5. *Retrospective alcohol use.* We will also collect more information on alcohol use over time using retrospective questions for participants at age 10-15, 20 and 25 using questions used in the European Investigation into Cancer and Nutrition (EPIC) study, which described the trends of self-reported past consumption of alcohol use (36). Retrospective alcohol use will be modified to create an average number of drinks per week at age 10-15, 20, and 25. This measure will provide information on alcohol use over time.

6. *Biomarkers of chronic excessive drinking.* We will use the EtG in hair and the PEth in whole capillary blood. Two locks of hair (alternatively arm/chest hair) will be collected to assess EtG, and a capillary blood sample on a dried blood spot will be taken to measure PEth. Both biomarkers will be analyzed by liquid chromatography coupled to tandem mass spectrometry using ISO-validated methods. EtG and PEth are two recent biomarkers that appear especially reliable (9,37,38), whereas traditional biomarkers (carbohydrate-deficient transferring and gamma-glutamyl-transferase) lack sensitivity and/or specificity, especially among young people showing a typical RSOD behavior on weekends or special occasions. Hair EtG is efficient to detect alcohol abuse and cut-offs have been proposed for at-risk drinkers (> 20/30 g of ethanol/day) and heavy drinkers (> 60 g of ethanol/day). Its sensitivity and specificity are very high (> 95%). On the contrary, it is less reliable for low levels of alcohol use. By contrast, PEth is useful to detect low levels of alcohol use during the last two to four weeks. Indeed, PEth has demonstrated a very high specificity (theoretically 100%).

Secondary endpoints

1. *Risky single-occasion drinking*. RSOD is often measured with an ordinal scale (e.g. "*no RSOD*," "*less than monthly RSOD*," "*monthly RSOD*," "*weekly RSOD*," and "*daily RSOD*") and with a cut-off of five or six drinks on a single occasion (39). The current study will propose more precise operationalization of RSOD (e.g., number of drinks per occasion, duration of each occasion, and continuous scale for number of occasions).

2. *Health issues and illnesses*. The Short Form Health Survey (SF-12, 40) will be included with its two subscales: the mental component summary (mental and social health), and physical component summary (physical health).

3. *Consequences*. Sixteen consequences already used in C-SURF, which are not explicitly substance-related (41), will be selected from standard instruments (42–45). Two sum-scores of consequence-associated scores will be computed: the first for social consequences and the second for health consequences. In addition, alcohol-related consequences will be assessed as in the DSM-5 (10).

4. *Quality of life*. The World Health Organization Quality of Life Instrument (WHOQoL-BREF) has been validated widely, and it was found to be reliable and valid for use among patients with alcohol-related dependence (46). There are 26 questions rated on a five-point scale composed by two general question of quality of life and four dimensions: physical health (seven items), psychological health (six items), social relationships (three items) and environment (8 items). Each question was rated in reference to the last two weeks. A percentage rating within each domain is computed with scores ranging from zero (lowest QOL) to 100 (highest QOL).

5. *Life satisfaction*. The Satisfaction With Life Scale (SWLS) will be use to assess life satisfaction (47). A mean score of the five questions of the SWLS will be computed.

Other variables

For the selection of participants, we will use the AUDIT (26,27). The AUDIT is a ten-item screening measure for AUD (48,49) developed by the World Health Organization, which includes three questions on dependence, four questions on specific consequences of harmful alcohol use, and three questions on hazardous alcohol use. It has been described as a reliable screening tool of AUD (50).

We will also assess demographic variables: age, educational status, and professional status.

Based on the C-SURF data (three waves already collected and available), we will match information on demographics, health, and substance use.

Ethical aspects and safety

Consent and risks

All procedures performed in studies involving human participants will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol, information letters, questionnaires, and the informed consent forms of the study have been approved by the Human Research Ethics Committee of the Canton of Vaud, Switzerland (no. 2017-00776). There is no expected adverse event or side effect for participants. Informed consent will be obtained from all individual participants included in the study.

Confidentiality of the data

Data generation, transmission, storage, and analysis of health-related personal data and the storage of biological samples within this project will strictly follow the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5. Data protection and confidentiality will be guaranteed.

Patient and Public Involvement

Patients and public were not involved.

Statistical analysis

Sample size

There is no available information about the psychometric properties of the self-reported AUD nor of HAU. Therefore, it was not possible to estimate a precise sample size in a power calculation. To ensure that we have enough alcohol-related dependent participants to test the hypothesis of HAU being equivalent or better than self-reported AUD, we made several sample size calculations based on different scenarios of possible sensitivity of self-reported AUD (sensitivity between 0.2 and 0.8) using a proportion non-inferiority test with alpha=5%, a margin of equivalence of 10%, and a difference in sensitivity between self-reported AUD and HAU of 5% (51). The worst scenario is for sensitivity around 50% and no correlation between self-reported AUD and HAU. In this worst scenario, for a power of 80%, 135 alcohol-related dependent participants are needed (as shown in Figure 2). In a favorable scenario, with a power of 80% and a middle/large correlation (supported by the C-SURF data: r=0.50), a total of 67 participants with alcohol-related dependence are needed. We decided to choose a scenario between the worst and the most favorable with a correlation between self-reported AUD and HAU of 0.35, which is a moderate correlation between two related but different concepts. In this scenario, 86 participants with alcohol-related dependence are needed. Therefore, we will select at least 86 participants with alcohol-related dependence and 86 participants without alcohol-related dependence.

[Figure 2 about here]

The AUDIT score will be used to select participants. Alcohol-related dependence is defined with a cut-off of 13 at AUDIT (52), with a sensitivity ranging between 0.78 and 0.90 and a specificity ranging between 0.87 and 0.92 (50,52). The positive predictive values were estimated between 0.40 and 0.88 (50,52). Thus, by randomly selecting 151 participants with AUDIT greater or equal to 13 and a positive predicted value of 0.64 (mid-point between 0.40 and 0.88), there is a 95% probability of selecting at least 86 participants who are true positive. The negative predictive values were estimated at 0.97 (50,52). Therefore, we will select 93 participants with AUDIT lower than 13 in order to have a 95% probability of selecting at least 86 true negative non-alcohol dependent participants. The psychologists will be blinded to the participants' AUDIT scores. In order to avoid issues related to attrition, we added 15% of participants in each group, a total of 173 participants with AUDIT≥13 and 107 participants with AUDIT<13 will be invited in each group (n=280).

Data Analyses

Analyses 1 (primary outcomes): HAU and AUD as measures of alcohol-related dependence

Considering the clinical interviews as a gold standard of alcohol-related dependence, and biomarkers as a gold standard of chronic excessive drinking, we will test the diagnostic performance of self-reported AUD and HAU measures to see whether they are suitable ways to assess alcohol-related dependence. We will use effect sizes to compare the correlations (R^2 to test common variance between measures and clinical effect size), and we will use Fisher's R to Z transformations to compare whether the correlations are significantly different from one another. Then, we will use dichotomized variables and test sensitivity, specificity, positive predicted value, and negative predicted value using the receiver operating characteristic (ROC) curves. To dichotomize alcohol use, different theory-oriented cut-offs

will be compared (four, two, and one drink(s) per day), and data-driven models will also be tested using stratum specific likelihood ratio analysis and machine learning (random forests).

Analyses 2 (primary and secondary outcomes): associations with health outcomes and alcohol-related variables

We will compare outcomes' associations with the gold standards and the different self-reported measures (HAU, self-reported AUD, and self-reported AUD without consequences). Effect sizes will be compared in order to know which measure is the best predictor of health and psychosocial issues and which one most resembles the associations with the gold standards.

Analyses 3 (secondary research question): association of RSOD with alcohol-related dependence

Associations of RSOD with the gold standard of alcohol-related dependence will be performed, adjusting for alcohol use (extended QF questionnaire) to assess its independent effect, and including an interaction between alcohol use and RSOD to investigate their combined effect.

Analyses 4 (secondary research question): cut-off for biomarkers and associations with RSOD

The diagnostic performance of EtG and PEth will be calculated for their optimal cut-off values selected with the ROC curves. Comparisons with clinical interviews, and HAU will be performed. We will also test whether EtG and PEth are potential measures of RSOD, using EtG and PEth cut-offs to predict RSOD using correlations and ROC curves. Different cut-offs will be tested in these analyses.

Analyses 5 (secondary research question): non-response bias

We will compare non-respondents to respondents using the information available in the previous waves of the C-SURF study using logistic regressions.

All analyses will use a two-sided $\alpha=0.05$. Statistical software will include SPSS, Stata, and R.

Discussion

The main aim of this study is to test the quality of the self-reported AUD (also focusing on primary symptoms and excluding alcohol-related consequences) and of the self-reported HAU as measures of alcohol-related dependence as defined by the DSM-5 in a general population. The psychometric properties of the self-reported AUD and of the HAU will be tested against a clinical interview designed to diagnose alcohol-related dependence.

From an international perspective, the proposed project aims to address some methodological issues highlighted in recent studies related to the measure of substance-related dependence, and more specifically, alcohol-related dependence. The project will provide evidence regarding two important issues. First, it will test whether self-reported AUD, which is extensively used in alcohol research, is a reliable way to assess alcohol-related dependence. Second, it will investigate whether HAU is a reliable measure of alcohol-related dependence. Therefore, the study will provide insights on its capacity to capture alcohol-related dependence. The results of the study may have a large impact on future research on alcohol. It will suggest a better way to assess alcohol-related dependence in population-based samples and for screening perspectives. Additionally, the project will investigate thresholds needed for decision making (early intervention and treatment), test the effect of drinking patterns on self-reported AUD, and determine cut-offs for biomarkers. These cut-offs will be useful for legal medicine, which needs further studies for decision making regarding alcohol abstinence.

From a national perspective, this study will provide a valid prevalence rate of alcohol-related dependence among French-speaking young Swiss men in their middle-20s. It will be useful from a public health point of view. Moreover, cut-offs for unhealthy alcohol use will be

proposed, which may be relevant for preventive purposes and may identify at-risk youths in Switzerland. It will improve screening for unhealthy alcohol use. It would also be useful for general practitioners to detect alcohol-related dependent persons (53).

The current study is designed to provide evidence regarding the assessment of alcohol-related dependence in the general population and especially among young people. Potential benefits to society include a better understanding and evaluation of alcohol-related dependence, improvements of practices, and future development of adequate public health planning. It will help to identify at-risk persons and groups. It may change the practices from a clinical and public health perspective, such as the use of alternative measures to screen for alcohol-related dependence and identify at-risk alcohol users, and from a research perspective, for example to stop using unreliable self-reported addiction scales and thus to provide strong support to future findings in alcohol research.

List of abbreviations

AUD: Alcohol use disorder

AUDIT: Alcohol Use Disorder Identification Test

CHUV: Centre Hospitalier Universitaire Vaudois (Lausanne University Hospital)

C-SURF: Cohort Study of Substance Use and Risk Factors

DIGS: Diagnostic Interview for Genetic Studies

DSM: Diagnostic and Statistical Manual of Mental Disorders

EPIC: European Investigation into Cancer and Nutrition

EtG: Ethylglucuronide

HAU: Heavy alcohol use

PEth: Phosphatidylethanol

QF: Quantity-frequency

QOL: Quality of life

RSOD: Risky single-occasion drinking

SF-12: Short Form Health Survey

SNF: Swiss National Foundation

ROC: Receiver operating characteristic

SWLS: Satisfaction With Life Scale

WHOQOL: World Health Organization Quality of Life

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol, information letters, questionnaires, and the informed consent forms of the study have been approved by the Human Research Ethics Committee of the Canton of Vaud, Switzerland (no. 2017-00776). There is no expected adverse event or side effect for participants. Informed consent will be obtained from all individual participants included in the study.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KI and SB wrote the manuscript. All authors critically reviewed the manuscript for important intellectual content. The study design and research proposal were mainly developed by SB and KI. GG, FS, and JBD made substantial contributions to the conception and the design of the study. The intervention was developed by SB and KI. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the final manuscript.

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Figure legends

Figure 1 legend: C-SURF: *Cohort Study of Substance Use and Risk Factors****; AUDIT:*** *Alcohol Use Disorder Identification Test.*

Figure 2 legend: AUD sens: *Alcohol use disorder sensitivity;* ***HAU sens:*** *Heavy alcohol use sensitivity; cor: correlation.*

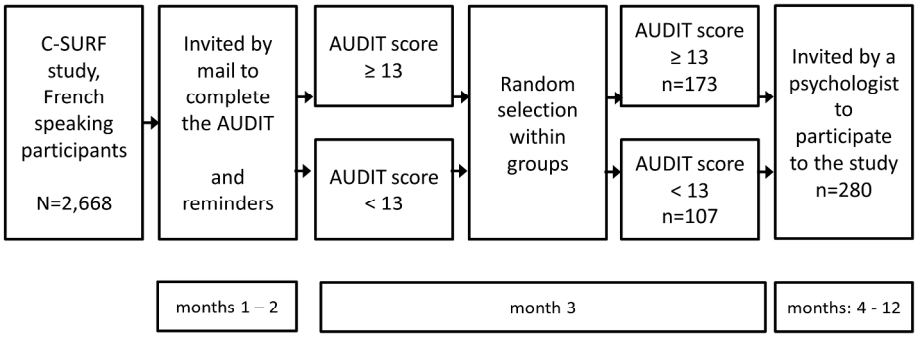

Figure 1 legend: C-SURF: Cohort Study of Substance Use and Risk Factors; AUDIT: Alcohol Use Disorder Identification Test.

254x190mm (300 x 300 DPI)

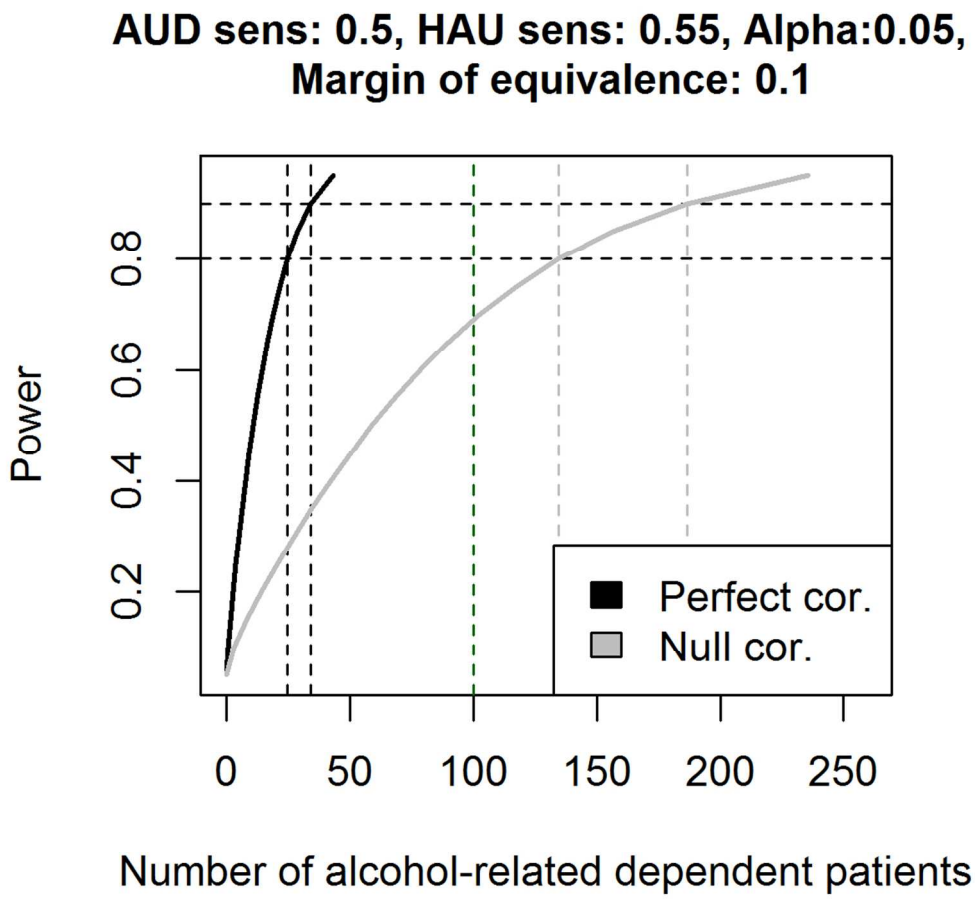

Figure 2 legend: AUD sens: Alcohol use disorder sensitivity; HAU sens: Heavy alcohol use sensitivity; cor: correlation.

101x101mm (300 x 300 DPI)

Correction: *Comparison of self-reported measures of alcohol-related dependence among young Swiss men: a study protocol for a cross-sectional controlled sample*

Iglesias K, Sporkert F, Daeppen J, *et al*. Comparison of self-reported measures of alcohol-related dependence among young Swiss men: a study protocol for a cross-sectional controlled sample. *BMJ Open* 2018;8:e023632. doi: 10.1136/bmjopen-2018-023632

This article was previously published with an error.

Reference 16 "Studer J, Baggio S, Mohler-Kuo M, *et al*. Differential association of drinking motives with alcohol use on weekdays and weekends. *Psychol Addict Behav* 2014;28:651–8." was incorrect. The correct reference is:

Baggio S, Iglesias K, Studer J, *et al*. Is the relationship between major depressive disorder and self-reported alcohol use disorder an artificial one? Alcohol and Alcoholism 2015; 50:195–199.

BMJ Open 2019;**9**:e023632corr1. doi:10.1136/bmjopen-2018-023632corr1