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ASSESSING THE ASSOCIATIONS BETWEEN MENTAL DISORDERS, CARDIOVASCULAR RISK FACTORS, AND CARDIOVASCULAR DISEASE: THE COLAUS/PSYCOLAUS STUDY

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TABLE DES MATIÈRES

1 ABSTRACT

Background: Cardio-vascular diseases (CVD), their well established risk factors (CVRF) and mental disorders are common and co-occur more frequently than would be expected by chance. However, the pathogenic mechanisms and course determinants of both CVD and mental disorders have only been partially identified.

Methods/Design: Comprehensive follow-up of CVRF and CVD with a psychiatric exam in all subjects who participated in the baseline cross-sectional CoLaus study (2003-2006) (n=6'738) which also included a comprehensive genetic assessment. The somatic investigation will include a shortened questionnaire on CVRF, CV events and new CVD since baseline and measurements of the same clinical and biological variables as at baseline. In addition, pro-inflammatory markers, persistent pain and sleep patterns and disorders will be assessed. In the case of a new CV event, detailed information will be abstracted from medical records. Similarly, data on the cause of death will be collected from the Swiss National Death Registry. The comprehensive psychiatric investigation of the CoLaus/PsyCoLaus study will use contemporary epidemiological methods including semi-structured diagnostic interviews, experienced clinical interviewers, standardized diagnostic criteria including threshold according to DSM-IV and sub-threshold syndromes and supplementary information on risk and protective factors for disorders. In addition, screening for objective cognitive impairment will be performed in participants older than 65 years.

Discussion: The combined CoLaus/PsyCoLaus sample provides a unique opportunity to obtain prospective data on the interplay between CVRF/CVD and mental disorders, overcoming limitations of previous research by bringing together a comprehensive investigation of both CVRF and mental disorders as well as a large number of biological variables and a genome-wide genetic assessment in participants recruited from the general population.

2 BACKGROUND

Cardiovascular diseases (CVD) and mental disorders co-occur more frequently than would be expected by chance [1;2], but the reasons for this association are poorly understood.

Several studies have documented that the prevalence of depression is increased among patients with coronary artery disease (CAD) [3;4]. An even larger percentage of patients with CAD has subthreshold depressive syndromes [5], which have been associated with increased mortality [6]. Similarly, depression occurs in 20 to 50% of patients after an acute stroke [7], and the development of depression is associated with a poor functional prognosis and a negative impact on the patient's quality of life [7;8]. Population-based prospective studies of individuals with depression or depressive symptoms documented increased CVD morbidity and mortality in these individuals [1;4;7]. Two studies that included subthreshold depressive syndromes also suggested an association between these syndromes and myocardial infarction or cardiac mortality [9;10]. CAD was associated more strongly with major depressive disorder than with subthreshold depression, which suggests a dose response-relationship between depression and the development of CAD [11]. However, the large majority of these epidemiological studies relied on depression scales or self-rating questionnaires for depression, rather than on diagnostic interviews. These studies also did not take into account potential effects of comorbid mental disorders such as anxiety or substance use disorders. In their review and meta-analysis, van der Kooy et al. [1] could identify only four prospective community studies based on a standardized clinical interview to diagnose depression with respect to subsequent CVD risk: three assessed the relationship between depression and the risk of coronary heart disease [9;10;12] and one the relationship between depression and stroke [13]. As these studies could not or could only partially adjust for the presence of established physical or behavioral cardiovascular risk factors (CVRF), the role of depression as an independent risk factor for CVD is debatable [4].

Several studies also suggested that anxiety symptoms, "worry" and specific anxiety disorders may influence the prognosis in patients with established coronary heart disease and promote the development of cardiovascular events in healthy participants [2;14]. However, with the exception of the study of Weissman et al. [15], existing research was based on anxiety scales and not on structured psychiatric interviews designed to assess the four major subtypes of anxiety disorders (panic disorder, generalized anxiety disorder, agoraphobia and social phobia). Hence, whether there is an unspecific effect of anxiety or worry related to all forms of anxiety disorders or, alternatively, whether specific anxiety disorders are differentially associated with CVD remains an open question [16].

Finally, mental disorders have been associated with CVRF such as heavy smoking, diabetes [17;18], insulin resistance [19] and obesity [20;21]. Similarly, prospective cohort studies found ApoE4, hypertension during mid-life, heart failure, smoking, adiposity, increased cholesterol blood level and diabetes to be associated with an increased risk for Alzheimer's disease [22], vascular dementia [23;24] and mild cognitive impairment [25], but the precise impact of CVRFs on cognitive function awaits further investigation.

Hence, the primary aim of this study is to prospectively assess the complex interplay between CVD, CVRF and mental disorders, based on the follow-up of a large population-based cohort with a comprehensive somatic, psychiatric and genetic investigation at baseline. The main research questions are 1) Do mental disorders increase vulnerability to CVRF and CVD? 2) Do CVRF and CVD or their drug treatment promote the development of mental disorders? and 3) Do CVRF/CVD and mental disorders share common pathogenic processes?

3 METHODS / DESIGN

The cohort includes all participants of the original CoLaus sample (n = 6'738) [26], a majority of which also underwent a thorough psychiatric examination [27]. A first 5-year follow-up combining a comprehensive CVRF and CVD assessment with a psychiatric exam is currently ongoing and further follow-up investigations are planned in a five-year rhythm. This protocol describes details of the first follow-up (2009-2012)

3.1 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria: participation in the baseline CoLaus study [26] and willingness to participate to the follow-up.

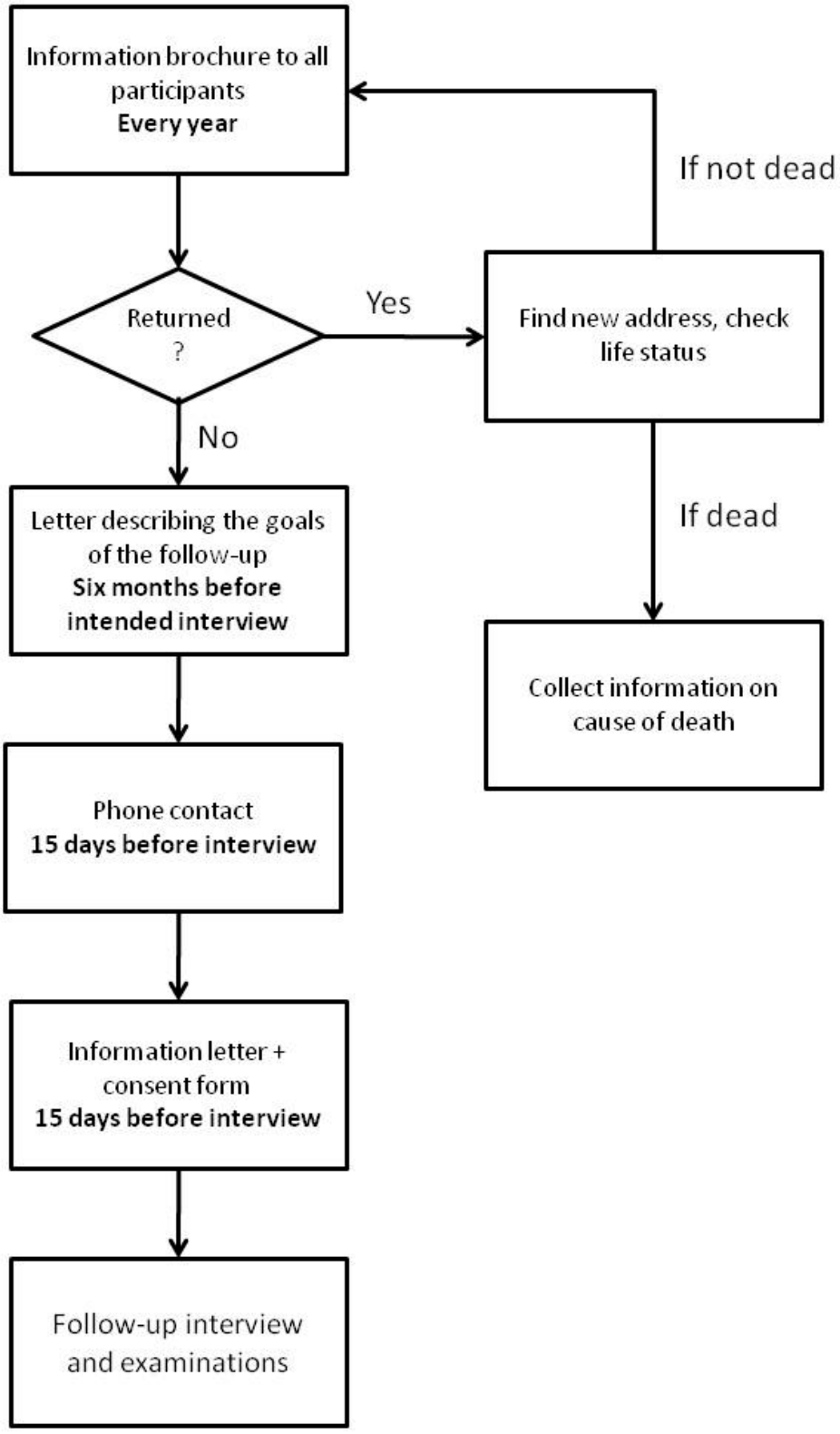
Exclusion criteria: refusal to participate, having moved too far away to come to the somatic exam at the CHUV in Lausanne, insufficient ability to speak French or English (for the psychiatric part only).

3.2 CONTACT AND FOLLOW-UP

All participants of the baseline examination received an information brochure summarizing the preliminary study results; in case of returned mail, information from phone companies or the population register of the City of Lausanne was used to find the new address of the participant or to confirm that the participant has died. In order to maximize follow up, letters and brochures will be sent to participants at six-month intervals. Six months before the intended follow-up interview, a letter describing the goals of the follow-up, the requirements for participation and the importance of their contribution to long-term efforts in disease prevention, has been sent to participants. In a second step, participants will be contacted by phone to provide further information on the study. Prior to the follow-up interview, participants will receive the detailed information letter and consent forms. **Figure 1** summarizes the different steps to contact participants.

Given that more than 95% of CoLaus participants indicated that they were willing to take part in the follow-up, we expect a sample of 6'000 participants between 40 to 80 years of age taking part in the somatic exam (and 4'000 to both the somatic and psychiatric exam). We expect that approximately 3'500 participants will have the combined evaluation at baseline and at follow-up. For the second (i.e. 10-year) follow-up, we expect a sample of about 5'400 individuals for the somatic exam and a subsample of 3'600 with at least two psychiatric evaluations. The increased sample size for the subsample with combined somatic and psychiatric evaluations at the 10-year follow-up is due to the inclusion of the 65 to 75 year-old participants at baseline in the psychiatric evaluation at the 5-year follow-up. As demographic data of all the residents of the city of Lausanne in the age range of interest are known, the demographic characteristics of participants and non-participants can be compared.

Figure 3. Flowchart for the follow-up of the CoLaus/PsyCoLaus participants.



3.3 CLINICAL (SOMATIC) ASSESSMENT

Similarly to the baseline evaluation [26], the follow-up somatic investigation will be conducted at the CHUV in Lausanne and will include an interview, a physical exam, blood and urine collections as well as a list of questionnaires with supplementary information on self-report dietary habits, physical activity, sleep patterns and disorders. Additional information will be abstracted from the medical records or collected from the death registry, whenever appropriate. We will use the same definitions for CVRF at follow-up as at baseline, in order to determine the incidence of these CVRF.

Weight, height, waist and hip circumferences, percent body fat (bioimpedance), blood pressure and heart rate will be measured. Blood will be taken in the fasting state and analyses be performed at the Central Chemistry Laboratory and the Laboratory of Endocrinology of the CHUV. Most of the blood and urine markers will be identical to those measured at baseline (**Table 1**). Aliquots of plasma, serum and urine will be stored at -80°C for future analyses. The following definitions will be applied: overweight, body mass index (BMI) ≥ 25kg/m²; obesity: BMI ≥30 kg/m²; hypertension, blood pressure ≥ 140/90 mmHg and/or presence of anti-hypertensive drug treatment; low HDL cholesterol, (<1 mmol/L in men and <1.29 mmol/L in women); high LDL cholesterol: ≥ 4.1 mmol/L; high triglyceride, ≥ 2.2 mmol/L. Dyslipidemia will be defined by low HDL cholesterol and/or high triglyceride and/or LDL cholesterol ≥ 4.1 mmol/L or ≥ 2.6 mmol/L in presence of self-reported myocardial infarction, stroke, coronary artery disease or diabetes. Diabetes will be defined by fasting plasma glucose ≥ 7 mmol/L and/or presence of oral hypoglycaemic or insulin treatment.

Dietary intake will be assessed with a self-administered semi quantitative food frequency questionnaire which covers the 4 weeks prior to the day of data collection. The questionnaire was developed and validated in the general adult population of Geneva, Switzerland [28;29]). It includes a list of about 80 food items and their serving sizes, and food intake data can be converted into daily energy and nutrient intakes.

Physical activity will be assessed with a validated, self-administered quantitative physical activity frequency questionnaire developed in the Geneva general adult population [30]. The questionnaire covers the last 7 days prior to the day of data collection. The French version [31] of the Center for Epidemiologic Studies Depression Scale (*CES-D*) [32], a 20 item instrument will be used to assess the severity of self-report depressive symptoms over the past week on a 4-point scale.

Cognitive function will be assessed by the Mini Mental State Examination (MMSE) [28;33]. The test is used to screen for cognitive deficiency, to evaluate its intensity and to measure changes in states of confusion and dementia in older participants; the French translation has been validated [34].

Sleep disorders will be assessed by a series of questionnaires. Daytime sleepiness will be assessed by the Epworth Sleepiness scale (ESS) [35], a self-administered questionnaire measuring the participant's general level of daytime sleepiness. ESS scores distinguish normal participants from patients in various diagnostic groups including those with obstructive sleep apnea syndrome, narcolepsy and idiopathic hypersomnia. Sleep apneas will be assessed by the Berlin questionnaire [36], which surveys the presence and frequency of snoring, daytime sleepiness or fatigue and high blood pressure. Circadian typology (i.e. "morningness" and "eveningness" of the participants) will be assessed by the validated French translation [37] of the Horne-Ostbergs Morningness-Eveningness Score [38]. Narcolepsy will be assessed by the Ullanlinna Narcolepsy Scale [39], an eleven item, self-administered questionnaire. Sleep quality and

disorders for the month preceding the evaluation will be assessed by the Pittsburgh Sleep Quality Index (PSQI) [40], a self-administered questionnaire on participant's sleep quality, sleep duration, efficiency, use of hypnotics and poor daytime functioning.

The presence of restless leg syndrome (RLS) will be screened using a self-administered questionnaire based on the 4 basic diagnostic criteria of RLS developed during and international workshop and approved by the International Restless Legs Syndrome Study Group [41].

Persistent pain will be screened with the self administered TNS Sofres questionnaire [42] assessing the presence of pain for more than 3 months and its localization. This instrument has already been applied in a population based study [43].

3.4 PSYCHIATRIC ASSESSMENT

All interviews will be carried by psychologists or psychiatrists. The interviewers demonstrated an adequate inter-rater reliability following individualized training. This includes ratings of tapes and supervised co-ratings of live participants. In order to provide ongoing supervision throughout the study, each interview will be reviewed by an experienced psychiatrist or psychologist.

Diagnostic assessment will be performed by the follow-up version of the Diagnostic Interview for Genetic Studies (DIGS) [44]. This instrument is a shortened interim diagnostic interview based upon the chapters of the original DIGS to collect information on psychopathological manifestations and psychotherapeutic and drug treatment during the follow-up period. The DIGS elicits a wide spectrum of DSM-IV Axis I criteria including mood, anxiety, psychotic and specific substance use disorders as well as suicidal behavior. The French version of the DIGS was established in a collaborative effort from sites in France (INSERM, Paris) and Switzerland. Inter-rater and test-retest reliability of the French version were established in a clinical sample in Lausanne [45]. Excellent inter-rater reliability was found for schizophrenia, bipolar disorder, major depression and unipolar schizoaffective disorder while fair inter-rater reliability was demonstrated for bipolar schizoaffective disorder (**Table 1**). High kappa coefficients for inter-rater reliability and slightly lower kappas for test-retest reliability were also found for drug and alcohol use disorders as well as for antisocial personality diagnoses [46]. Reliability was also established for subthreshold depressive (Yule's Y=0.91) and manic (Yule's Y=0.89) syndromes.

The measurement of cognitive functioning in participants aged 65 to 80 years will rely on several instruments. Subjective cognitive complaints will be assessed using the Cognitive Complaint Questionnaire [47]**.** Objective cognitive assessment will comprise a series of specifically designed tests to ascertain a wide range of cognitive functions taking into account both education and age-related performance: Do 80 (Epreuve de dénomination orale d'images) [48], Grober and Buschke episodic memory test [49], CERAD praxis items [50], lexical and semantic fluency tasks [51] and Stroop color test [52]. Severity staging will be performed using the Clinical Dementia Rating (CDR) [53].

Migraine will be assessed by the 'Diagnostic Interview for Headache Syndromes' (DIHS) and the specific headache subtypes will be characterized according to the criteria of the International Headache Society [54]. This instrument was developed by Merikangas et al. as part of an international collaborative study of chronic daily headache [55].

Life events that have occurred since the first investigation will be assessed by the short interview of F. Amiel-Lebigre [56]. In addition, subjects will complete a self-report battery including the Symptom Check List 90 Revised (SCL-90 R) [57], the Type D Scale (DS14) [58], the Hypomania Checklist (HCL-32-R1) [59], the Social Support Questionnaire (SQQ6) [60], the Manchester Short Assessment of Quality of Life (MANSA) questionnaire [61] and the Revised NEO Personality Inventory (NEO-FFI-R) [62].

At the end of the interview, participants will receive little swabs (Salivettes, Sarstedt, Leicester, UK) to be used for salivary cortisol collection the next working day at awakening, 30 minutes thereafter, at 11:00 a.m. and at 8:00 p.m. Free cortisol levels will be assessed using a chemiluminescence assay as described previously [63;64]. The list of all the psychiatric tools to be used is summarized in **table 2**.

Table 1 Somatic assessment at baseline and follow-up

Module	Variable	Baseline	Follow-up
1. Interview	a. Age, gender, origin, ethnicity (up to grandparents)	X	
	b. Education level, occupation, socio-economic status	X	
	c. Smoking, alcohol intake, physical activity	X	X
	d. Personal and family history of CVD, hypertension, diabetes, stroke, myocardial infarction, and coronary procedures or surgery.	X	X
	e. Current medication (over the counter or prescription)	X	X
	f. Diagnostic Interview for Headache Syndromes (DIHS) / Migraine	X	X
2. Physical exam	a. Height, weight, waist and hip circumference	X	X
	b. Blood pressure (triplicate measurement with automated device), heart rate	X	X
	c. Percent fat (bio impedance)	X	X
3. Blood (fasting)	a. Markers of diabetes and insulin resistance: glucose, insulin, leptin, adiponectin	X	X
	b. Makers of dyslipidemia: total, HDL and LDL-cholesterol, triglycerides, LDL-size[1], ApoB[1]	X	X
	c. Biomarkers associated with increased CVD risk: CRP, homocystein[1], TNF-α[2], IL-6[2], IL-1β[2]	X	X
	d. Markers of co-morbid conditions:	X	X
	i. Liver function tests: ASAT, ALAT, γ-GT, alkaline phosphatase	X	
	ii. Renal function: creatinine	X	X
	iii. Chronic elevated alcohol consumption: carbohydrate deficient transferin	X	X
	iv. Others: uric acid, calcium, albumin[1], total proteins	X	X
	e. Blood count		X
4. Urine	a. Microalbuminuria, Creatinine	X	X
5. Saliva	a. Four salivary cortisol measures		X

[1] only baseline; [2] retrospectively assessed for baseline

ALAT, Alanine Aminotransferase; ApoB, apolipoprotein B; ASAT, Aspartate Aminotransferase; CRP, C-reactive protein; CVD, cardiovascular disease; γ-GT, gamma-glutamyl transpetidase; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination; TNF-α , Tumor Necrosis Factor-alpha

Table 2 Psychiatric assessment tools at baseline and follow-up.

Module	Instrument / Assessed domain	Baseline	Follow-up
1. Interview	a. Diagnostic Interview for Genetic Studies (DIGS) / DSM-IV Axis-I diagnoses	X	X
	b. Short interview of F. Amiel-Lebigre / Life events	X	X
	c. Family History-Research Diagnostic Criteria (FH-RDC) / DSM-IV Axis-I diagnoses in 1st-degree relatives	X	
3. Cognitive tests	a. Mini Mental State Examination (MMSE)	X	X
	b. Cognitive Complaint Questionnaire		X
	c. Do 80 (Epreuve de dénomination orale d'images)		X
	d. CERAD praxis items		X
	e. Stroop color test		X
	f. Clinical Dementia Rating (CDR)		X
4. Self ratings	a. General Health Questionnaire, 12 question version (GHQ-12) / Screening of psychiatric disorders	X	
	b. State-Trait Anxiety Inventory (STAI) / Anxiety level	X	
	c. Retrospective Self Report Childhood Inhibition (RSRCI) / Childhood inhibition	X	
	d. Dimensions of Temperament Survey (DOTS) and DOTS Revised (DOTS-R) / Temperament	X	
	e. Eysenck Personality Questionnaire (EPQ) / Personality dimensions	X	
	f. Type A / Type A behavior	X	
	g. Sensitivity to Reward (STR) / Sensitivity to reward	X	
	h. Parental Bonding Instrument(PBI-M, PBI-F) / Perception of parenting style	X	
	i. FACES III / Family adaptability and cohesion	X	
	j. Dyadic Adjustment Scale (DAS) / Marital adjustment	X	
	k. Family Attitude Scale (FAS-30) / Emotional climate in family	X	
	l. Euronet: Problem Resolution Strategy / Coping	X	
	m. MOS-Sleep Module / Quality of sleep	X	
	n. Center for Epidemiologic Studies Depression Scale (*CES-D*) / Depression symptoms		X
	o. Symptom Check List 90 Revised (SCL-90 R) / Psychiatric symptoms		X
	p. Hypomania Checklist (HCL-32-R1) / Hypomania symptom screening		X
	q. Revised NEO Personality Inventory (NEO-FFI-R) / Personality dimensions		X
	r. Type D Scale (DS14) / Type D behavior		X

s.	Social Support Questionnaire (SQQ6) / Social support	X
t.	Manchester Short Assessment of Quality of Life (MANSA) / Quality of life	X

3.5 VALIDATION OF INCIDENT EVENTS

If a participant indicates that she/he was treated during the follow-up interval, relevant diagnostic and treatment information will be elicited from the patient's physician or hospital medical records including information from coronary angiogram procedures, coronary artery bypass surgery or peripheral artery disease. The diagnosis of specific CVD will rely on the following definitions:

- Myocardial Infarction: hospital discharge diagnosis (HDD) indicating typical ECG and elevated myocardial enzymes.
- Acute coronary syndromes: HDD providing evidence of typical electrocardiographic changes or coronary angiogram or history of percutaneous transluminal coronary angioplasty.
- Stroke: HDD describing the occurrence of new neurologic deficits lasting more than 24 hours.

All medical records compatible with CVD will be thoroughly reviewed by a cardiologist. Diagnosis of CVD will be based on all available information and established by a local adjudication committee according to international recommendations [65]. In case of doubts, senior physicians who have been involved in the participant's treatment will be contacted for the collection of additional information and reviewed by the local adjudication committee.

Deaths within the cohort will be determined every year comparing the CoLaus database with the Lausanne City Registry of inhabitants. Information on the cause of death will be elicited from the Swiss National Death Registry and, if available, from primary care physicians or hospital charts. Complementary data will be collected from relatives where necessary. The definition of CVD death will encompass fatal MI, stroke, fatal cardiac arrhythmia, peripheral artery disease (aortic dissection).

3.6 MANAGEMENT

The coordination of the ascertainment of participants as well as the progress of data analyses will be monitored by several committees:

- The local steering committee will be in charge of data collection and data management including the training and supervision of staff involved in the ascertainment of participants.
- The scientific committee will include all investigators. The scientific committee will meet twice a year and be in charge of the scientific aspects of the project and ensure its multicenter character. Specifically, this committee will a) decide on the timing and distribution of analyses across centers; b) supervise the local steering committee to ensure recruitment progression and c) evaluate the feasibility and scientific value of complementary subprojects submitted by researchers from outside, intending to use parts of collected follow-up data.
- An international advisory board will include all principal investigators as well as international specialists with a large scientific expertise in cardiovascular and psychiatric epidemiology or population genetics. The international advisory board will meet once a year to monitor the scientific progression of the project and to enhance international collaboration.

3.7 STATISTICAL POWER ANALYSES

The power calculations for the associations between psychiatric risk factors at baseline and cardiovascular outcomes (CVRF or CVD) are summarized in **table 3**. Power calculations were based on the formula for dichotomous variables [66]. We assume a two-tailed p-value of 0.05 and an attrition of 10% per follow-up resulting in a sample of 3'400 individuals at the 5-year and 3'600 individuals at the 10-year follow-up. These calculations take into account a 45% prevalence of lifetime diagnosis of depression at baseline. As participants already presenting with specific CVRF at baseline need to be excluded from these analyses, the calculated sample size was reduced accordingly (i.e. 15.7% for obesity, 36.7% for hypertension, 34.2% for dyslipidemia and 6.6% for diabetes). Moreover, the expected occurrence of new specific CVRF during the follow-up interval was calculated under the assumption that age-specific prevalence rates of CVRF at follow-up in non-depressed individuals remain the same as those at baseline, whereas the estimation of cardiovascular events was based on the recalibrated Framingham risk function [67]. The results indicate that after a 5-year follow-up, an association between depression at baseline and a 1.5-fold increased risk for the occurrence of hypertension or dyslipidemia in depressed individuals could be detected with a probability of more than 80%. For obesity and diabetes, the statistical power will be nearly 80% if the relative risk is at least 1.75. Regarding CVD, a doubled risk in depressed individuals at baseline would be detected with a probability of 72%. For a 10-year follow-up, a 1.5-fold increased risk for the four CVRF could be detected with probabilities ranging between 73% (obesity) and 100% (hypertension). A 1.75-fold and a two-fold increase of CVD events in depressed participants could be detected with probabilities of 80% and > 90%, respectively. Given that the three previous prospective studies [1;4;7] based on diagnostic interviews found at least a two-fold increased risk for CVD in depressive individuals, there is a satisfactory probability that such an increase in risk could be detected at the first follow-up examination. Similarly, a two-fold increased risk for diabetes [68] and obesity [69] in depressed participants has been reported, suggesting that this study has a high probability to detect such relationships at least at the second follow-up.

The power calculations for the associations between CVRF and CVD at baseline and incidence of psychiatric outcomes are summarized in **table 4**. The power calculation was based on the formula for dichotomous variables [66]. We assumed a two-tailed p-value of 0.05 and an attrition of 10% per follow-up. The power calculations were also based on the baseline prevalence of specific CVRF and participants with a lifetime diagnosis of depression at baseline (45%) were excluded from these analyses, resulting in a sample of 1'870 participants at the 5-year and 1'925 participants at the 10-year follow-up. The expected occurrence of new depressive disorders during the follow-up interval was based on the age-specific incidence rates of the population-based NEMESIS study [70]. In participants with obesity, hypertension or dyslipidemia at baseline, a 1.5-fold increased risk of depression would be detected with a probability >70% and 90% at the first and second follow-up, respectively. In participants with diabetes, a 1.75-fold increased risk for depression would be detected with a power of 72% at the first und 96% at the second follow-up. The statistical power for mental disorders other than depression is lower because of their lower prevalence in the sample. However, with almost 34% of affected participants, analyses including the overall category of anxiety disorders had only a marginally smaller power than those involving depression (not shown).

The power to detect differences between residents exhibiting a condition (specific mental disorder or CVRF) and those without this condition with respect to continuous outcome variables (e.g. scores or biological variables) was calculated according to the formula for continuous variables of Freeman [66]

and assuming a sample size of 3400. This power depends upon both the prevalence of the syndrome and the expected effect size in terms of standard deviation (SD). **Table 5** shows that even for rare conditions with a prevalence of 1% and 5%, the cohort provides sufficient power to detect distribution differences of 0.5 SD and 0.2 SD, respectively.

Table 3 **Power (%) for analyses including anxiety at baseline as independent variable and somatic cardiovascular risk factors or cardiovascular disease after 5-year and 10-year follow-up.**

	Cardiovascular risk factor									
	Obesity		**Hypertension**		**Diabetes**		**Dyslipidemia**		**CVD**	
Follow-up time (years)	5	10	5	10	5	10	5	10	5	10
Expected sample size	2909	2994	2395	2465	3177	3270	2286	2353	3400	3500
Expected number of cases with new CVRF among non anxious	44 (2.3%)	83 (4.2%)	130 (8.2%)	241 (14.8%)	48 (2.3%)	86 (4.0%)	104 (6.9%)	205 (13.2%)	25 (1.1%)	46 (2.0%)
Expected power (%)										
RR=1.25	16	26	39	66	17	27	32	58	11	17
RR=1.50	45	70	88	99	48	72	80	98	28	46
RR=1.75	73	94	99	100	77	95	98	100	50	75
RR=2.00	90	99	100	100	92	100	100	100	69	91

CVD, cardiovascular disease; RR, relative risk.

Table 4 **Power for analyses including somatic cardiovascular risk factors at baseline as independent variables and cardiovascular disease at the 5-year and 10-year follow-up as the dependent variable.**

	Obesity		Hypertension		Diabetes		Dyslipidemia	
Follow-up time (years)	5	10	5	10	5	10	5	10
Expected number of cases with new CVD among those not affected with the specific CVRF at baseline	47 (1.1%)	77 (2.0%)	27 (1.1%)	44 (2.0%)	58 (1.1%)	95 (2.0%)	27 (1.1%)	44 (2.0%)
Expected power								
RR=1.25	12	15	12	17	9	11	12	17
RR=1.50	29	41	31	46	20	27	31	46
RR=1.75	49	67	55	75	34	46	55	75
RR=2.00	68	85	75	92	48	64	75	92
RR=2.50	90	98	95	100	72	87	95	100

Table 5 **Power for the analysis with continuous outcomes (%).**

Prevalence of the disorder	Effect size $(\mu_1-\mu_2)/s$				
	0.1	**0.2**	**0.3**	**0.5**	**1.0**
1%	9	22	42	84	100
3%	17	52	86	100	100
5%	25	73	97	100	100
10%	43	94	100	100	100
15%	56	99	100	100	100
20%	66	100	100	100	100
25%	73	100	100	100	100

4 DISCUSSION

The combined CoLaus/PsyCoLaus cohort provides a unique opportunity to obtain highly informative prospective data on the interplay between CVRF/CVD and mental disorders. Indeed, CoLaus/PsyCoLaus is currently the only existing study that brings together: 1) a thorough somatic investigation of CVRF, 2) an interview-based psychiatric evaluation, 3) the assessment of a comprehensive array of biological variables and 4) an extensive genome-wide genotyping in a large sample recruited from the general population. With the recent rapid progress in identifying genetic markers for complex diseases, we anticipate that numerous genetic markers for the index diseases in this study can also inform on the mechanisms of the associations between CVD/CVRF and mental disorders, as well as to predict risk for the development of these conditions. This will also enable us to identify gene-environment interactions underlying these diseases. A better understanding of the psychological, physiological and behavioral links underlying these conditions is expected to result in the development of more specific and efficient strategies of prevention and treatment for both psychiatric and CVD/CVRF, two major elements of the burden of disease.

This study also provides an excellent opportunity to prospectively assess the long-term course and its determinants, clinical consequences as well as the type and duration of treatment of CVRF and mental disorders in the community. Service utilization patterns for these conditions will also provide important information for the development of health policy with focus on prevention. Indeed, regarding psychiatric conditions, follow-up data on the course of specific disorders in the general population based on large samples and contemporary methodology are still scarce. Moreover, the longitudinal data should also provide an important empirical basis for nosology.

The proposed study together with the results of the recently initiated family study of the first-degree relatives of the CoLaus/PsyCoLaus sample will largely contribute to a better understanding of the nature of the comorbid associations between specific mental disorders and both CVRF and CVD. The increased knowledge of the psychological, physiological and behavioral links underlying CVRF/CVD and mental disorders is expected to result in the development of more specific and efficient strategies of prevention and treatment of both psychiatric and CVRF/CVD, two major elements of the burden of disease.

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6 CONFLICT OF INTEREST

PV and GW received an unrestricted grant for GSK to build the CoLaus study. The other authors report no conflict of interest.

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