

Paracelsus 10,000: A Prospective Cohort Study Based On The Population of Salzburg, Austria. Rationale, Objectives And Study Design

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Research Article

Keywords: Paracelsus 10,000, epidemiological study, Salzburg, Austria, study design

Posted Date: August 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-740574/v1>

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Abstract

Paracelsus 10,000 is a prospective cohort study with the objective to investigate the health status of the population in and around the city of Salzburg. The focus lies on common non-communicable diseases, mainly cardiovascular and cerebrovascular diseases, and their risk factors in a population-based cohort aged between 40 and 70 years. Between the years 2013 and 2020, 10,062 randomly selected participants (w: 5,187, m: 4,875) were investigated, of whom 2,620 underwent an intensified examination. The program consists not only of medical examinations, but was extended to inventories on mental disorders, lifestyle including nutrition and physical activity. From all study participants biological samples were stored in a biobank at -80°C enabling future investigations of biomarkers and utilization of the whole spectrum of multi-omics. The first follow-up phase of the study has started in late 2020 and will allow us to investigate the development of common non-communicable diseases occurring over time in the cohort of the *Paracelsus 10,000* study. This gives the study a unique position within the framework of Austrian epidemiological research with the potential to gain new insight into the role of interaction between genetic predisposition and lifestyle factors for disease development in the Salzburg population. Obtaining high-quality epidemiological data is also of particular relevance for the development of evidence-based prevention strategies. This report describes rationale, objectives and design of the study and provides insight into the main characteristics of the study cohort.

Introduction

According to the Austrian Health Interview Survey from 2014, 79% of all Austrians perceive their own health as good or very good [1]. Between the years 1991 to 2014, life years in good health increased by 10.2 years in men (to 65.9 years) and 9.7 years in women (to 66.6 years). In the same period, life expectancy at time of birth increased by 6.6 years in men (to 78.9 years) and by 4.7 years in women (to 83.7 years) [1]. Therefore, life years in good health increased to a higher extent than life expectancy itself. Increasing awareness and improved therapies are regarded as main causes for reduced mortality due to e.g. cardiovascular diseases (CVD) in highly developed countries over the last decades [2].

Despite these impressive developments, some serious conditions, such as hypertension, diabetes, overweight/ obesity and atherosclerosis are not adequately addressed through early diagnosis, appropriate lifestyle changes and therapies, which still causes unnecessary early deaths and loss of life years in good health. According to a survey performed in 2010, 98% of interviewed Austrians regard hypertension as a serious health problem (i.e. they agree on an association of hypertension and heart attack) [3]. However, only 15% identified themselves as hypertensive [3], whereas studies showed that 38,1% of all subjects in Austria have a blood pressure higher than 140/90 mm Hg [4].

Globally, 18.6 million people died from CVD (primarily ischemic heart disease and stroke) in 2019 [5], while in Austria CVD accounted for 32,148 deaths (38.6% of all documented cases) in the same year [6]. The improved prognosis and treatment mentioned earlier are due to findings of epidemiological studies conducted in the 20th and early 21st century. According to the Global Burden of Diseases Study,

neurological disorders rank as the number one cause for disability adjusted life years (DALYs) (250.7 million) and as number two cause of deaths (9,4 million, 16,8% of global deaths and an increase of 36.7% between 1990 and 2015) [7]. Hitzl and colleagues state that the total number of ischemic strokes recorded in the Austrian Stroke-Unit Registry was 8,690 in 2012 and is expected to increase to 15,626 in the year 2075 (calculating with mean fertility, mean life expectancy, and mean immigration) [8]. Despite similar risk factors, such as high blood pressure, obesity, metabolic syndrome, diabetes, high blood cholesterol, lack of exercise, poor diet, smoking and excessive alcohol consumption, the incidence of CVD is decreasing, while the incidence of ischemic stroke is not. Austria is not the only country with this trend; a study in Sweden shows an increase in stroke incidences between the years 1983–1985, 1993–1995 and 2001–2002 [9]. In contrast, other studies demonstrate a decrease of stroke incidences e.g. in UK (between 1981–1984, 2002–2004) [10], Russia (between 1982–1992) [11], Italy (between 1989–2005) [12] and Estonia (between 1991–1992, 2001–2003) [13]. According to Béjot and colleagues [14], the geographical variations could be due to differences in local health care policy, genetic, meteorological and environmental factors or differences in distribution of vascular risk factors. He also points to a rising incidence of stroke in young adults in European countries, as well as in developing countries.

For the *Paracelsus 10,000* study, three studies served as templates for high-quality epidemiological research with a range of addressed health exposures and outcomes: 1) the Copenhagen City Heart Study, originally launched in 1975 with a cohort of 20,000 and a strong focus on cardiovascular risk factors and markers of aging [15], 2) the KORA (Cooperative Health Research in the Region Augsburg) research platform, which comprises 18,000 participants from different research pools. It was started in 1996 in Augsburg, Germany and focuses on CVD, environment and stress exposures [16] and 3) the SHIP study (Study of Health in Pomerania), which investigates common risk factors and diseases in two independent cohorts of the high-risk population of northeast Germany [17]. In 1997 a random sample of the first cohort (named SHIP) included 6,265 individuals in cities and communities of West Pomerania and later in 2008 a second independent sample of 8,016 eligible subjects was enrolled in the same area (named SHIP-TREND) [18]. The three mentioned studies differ in their special focus, yet in general, they all address a range of risk factors, exposures and outcomes, as does the *Paracelsus 10,000* study. In addition, the *Paracelsus 10,000* study is going to provide an in-depth analysis of genetic dispositions and their interactions with lifestyle factors such as diet, smoking, alcohol consumption, physical activity and cardiorespiratory fitness, as well as on socioeconomic factors and mental health. Due to the multi-disciplinary examinations of the first study phase, participants are very well characterized phenotypically and can be followed-up with targeted panels of examinations. This gives the study a unique position within the framework of the Austrian epidemiological research and might give new insight into correlations of risk factors, lifestyle habits and multi-omics. Epidemiological research e.g. on hypertension in the Salzburg population is missing so far, disclosing a gap in this region. This report is focusing on the rationale, objectives and design of the study, providing insight into the structure and extent of the project.

Methods

The *Paracelsus 10,000* study is a population based, prospective cohort study. A formative evaluation of required resources was completed in the years 2012 and 2013 and the project structure was established. Recruitment of participants started in April 2013 and was finished in March 2020, while examinations were performed throughout the whole study period from Monday to Friday (except during school holidays). Data collection was conducted by trained staff with a background in medicine, biology or sports science. Facilities for the study were kindly provided by the University Hospital Salzburg (Landeskrankenhaus and Christian Doppler Klinik), including a dedicated blood laboratory, examination rooms, office space and computer and waiting rooms for the participants.

2.1. Recruitment and characteristics of the study population

People living in the city of Salzburg and surrounding areas were randomly selected from the local population registry and invited by letter to participate in the study. We aimed to recruit equal numbers of men and women. The population was stratified by age with the goal to recruit about 50% of subjects in the age range between 50 and 59 years, 25% of subjects in the age ranges between 40 and 49 years and 25% of subjects in the age range between 60 and 69 years. Participation was voluntary and without financial reward, while participants benefited from a preventive medical check-up. Approximately 60,000 invitation letters were distributed, yet a certain ratio did not attain recipient due to changed address or death. In total, we examined 10,062 participants, of whom 286 were not randomly selected, but they had proactively approached the study and were included when they fulfilled entry criteria. Participants were stratified into two groups: 1) 40–69 years old participants who received the basic examination program (basic program) and 2) 50–59 years old participants who received the basic program and additional examinations (extended program). These subjects were randomly chosen from the pool of 50–59 years old participants. For reasons of optimal capacity usage, 610 participants received additional examinations on a voluntary basis, without being randomly selected for the examination program. For return rate and distribution of age, gender and program see Fig. 1, for the list of basic and extended examination, see Table 1. Even though single investigations had to be omitted in case of physical inability, there were no predefined exclusion criteria for the invited participants.

All participants signed an informed consent form that was approved by the local ethics committee (415-E/1521/3-2012).

To get an idea of characteristics of our study cohort, we conducted comparisons with the population of Austria and the country of Salzburg. Variables compared were sex, age, migration background, educational attainment, type of employment, degree of urbanization, smoking habits and physical activity. The information was extracted from a questionnaire answered by the participants. We used national official statistics by Statistik Austria as reference [19] to compare the data of our cohort. Whenever possible we excluded all age groups from the reference data that did not overlap with the age

range of 40 to 69 years. Detailed information about the reference data used and the matching of answer options can be found in the supplementary material.

2.2. Investigations

All examinations of an individual participant were carried out on the same day and due to a strict time schedule, each examination was conducted at the same time of the day. Besides a complete blood count and urinalysis, the following examinations were included in the study program:

Anthropometry and body composition

- Body height
- Body weight
- Abdominal circumference
- Body composition: Multiple frequency bioelectric impedance Analysis was performed while participants adopted a supine position with arms spread apart from the body and legs separated. Signal input and output electrodes were placed on the dorsum of the right hand and foot. Recording electrodes were placed at standard positions at wrist and ankle, the measurement was repeated three times, while participants were not necessarily fasting (Body Impedance Analyzer, Nutri Plus Data Input, Germany).
- DEXA-Scan X-ray densitometry for measuring bone mineral density and body composition (Hologic Discovery A, Hologic APEX, USA).

Laboratory parameters:

- Blood count:
Red blood cells (RBC), white blood cells (WBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, reticulocytes measured with Sysmex XN-1000 (Sysmex Austria GmbH).
- Coagulation:
Thrombin time (TT), partial thromboplastin time (PTT), prothrombin time (PT)/international normalized ratio (INR), fibrinogen, antithrombin III measured with BCS XP (Siemens Healthcare Diagnostics GmbH).
- Blood Sediment:
Red blood cells (RBC), white blood cells (WBC) measured with Sysmex XN-1000 (Sysmex Austria GmbH)
- Lipid metabolism:
Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apolipoprotein-B, apolipoprotein-AI, lipoprotein (a) measured with Cobas 6000 (Roche Diagnostics GmbH).

- Glucose metabolism:
Fasting blood glucose measured with Cobas 6000 (Roche Diagnostics GmbH), HbA1c measured with Cobas Integra 400 Plus Analyzer (Roche Diagnostics GmbH) and fasting insulin.
- Renal function:
Serum creatinine, glomerular filtration rate (eGFR), serum urea, serum electrolytes (Na, K, Cl, Ca, Mg, P), serum uric acid, urine chemistry (albumin, creatinine, albumin/creatinine ratio, total protein, glucose), urine sediment (specific weight, pH value, red blood cells (RBC), white blood cells (WBC), nitrite, total protein, glucose, ketone bodies, urobilinogen, bilirubin),, electrolytes (Na, K, Cl, Ca, Mg, P) in urine measured with Cobas 6000 (Roche Diagnostics GmbH) while urine sediment was measured with Cobas U 601 (Roche Diagnostics GmbH).
- Liver function:
Aspartate transaminase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (gGT), alkaline phosphatase (AP), cholinesterase (CHE) measured with Cobas 6000 (Roche Diagnostics GmbH).
- Pancreas function:
P-amylase, lipase measured with Cobas 6000 (Roche Diagnostics GmbH).
- Iron parameters:
Iron, transferrin, transferrin saturation, ferritin measured with Cobas 6000 (Roche Diagnostics GmbH).
- high sensitivity c-reactive protein (hsCRP), thyroid-stimulating hormone (TSH), prostate specific antigen (PSA, for men), total serum protein measured with Cobas 6000 (Roche Diagnostics GmbH).

Cardiovascular parameters:

- Blood pressure was measured bilaterally in a sitting position. The measurement was repeated three times with a previous resting period of each 60s (Watch BP office AFIB from the company Microlife AG Swiss Corporation, Switzerland).
- Electrocardiography (ECG) 12-lead, in a supine position ((Schiller Cardiovit AT-102 Plus 12-Kanal-EKG, Germany).
- Ankle–brachial pressure index was measured three times in a supine position (Boso ABI-system 100 PWV, Bosch + Sohn, Germany).
- 24 h blood pressure: A portable device was taken home by participants and measured blood pressure, pulse and pulse wave velocity in 15-minute intervals from 8 a.m. to 10 p.m. and in 30-minute intervals during night (Mobile-O-Graph PWA, Industrielle Entwicklung Medizintechnik und Vertriebsgesellschaft mbH (I.E.M.), Germany).
- Coronary Artery Calcium Score (Agatston-Score) using Computed Tomography (Siemens Somatom Definition AS+, Erlangen, Germany) [Agatston et al., 1990] [20].

Spirometry, measurement of liver stiffness, oral glucose tolerance test:

- Pulmonary function test was carried out, determining forced vital capacity and forced expiratory volume over 1s using a portable spirometer (Easy One™ Spirometer, nnd Medical Technologies, Zurich, Switzerland). The tests were performed in sitting position in triplicate with values being accepted when consecutive maneuvers yielded values within 10% of each other [Miller et al., 2005] [21]. Exclusion criteria were recent operations, cardiovascular and acute pulmonary diseases.
- Liver stiffness measurement and semi-quantitative estimation of fat content via continuation attenuated parameter using Fibroscan 530 Compact (Echosens Paris. France).
- An oral glucose tolerance test (OGTT) was performed following the standard protocol of the American Diabetes Association. Before and at 30min, 60min, 90min and 120min after oral intake of 75g glucose venous blood was drawn for measurement of plasma glucose and insulin levels.

Medical history

Trained staff conducted a face-to-face interview recorded as audio file that included medical history, family history and medication. Further inventories were merged to one computer-based questionnaire that was answered discretely by participants either in the study rooms (possibly with assistance by the staff) or at home. Participants who were not familiar with computer work or who needed translation answered the questionnaire manually and the study staff digitalized the data. The questionnaire included:

- ODQ-D (Oswestry Low Back Pain Disability) [Fairbank et al., 19080] [22]
- WOMAC (Western Ontario and McMaster Osteoarthritis Index) about cox arthrosis [Bellamy, 1995] [23]
- Screening questionnaire of the Austrian Social Insurance [24].

During the face-to-face interview, neurological diseases were surveyed [25] and the Salzburg Dementia Prediction Test was conducted [8]. The questionnaire filled out by the participant included further questions on epilepsy.

The interview also included questions on major depressive disorder, bulimia and anorexia nervosa, generalized anxiety disorder, manic and hypomanic episodes, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, substance and alcohol abuse. Additional inventories were answered by the participants at the computer:

- BDI (Beck Depression Inventory) slightly modified [Beck at al., 1961] [25].
- Barrat Impulsiveness Scale (BIS-15) [Patton et al., 1995; Spinella, 2007] [26; 27].

Ultrasound of the carotid arteries

- Ultrasound examination of the carotid artery bilaterally in a supine position (Panasonic Healthcare Diagnostics US). Intima media thickness and total plaque area were measured.

Assessment of lifestyle factors

Further inventories on lifestyle that were answered discretely by participants, were included:

- AUDIT (Alcohol Use Disorders Identification Test) [Saunders et al., 1993] [28]
- Inventory on diet according to the EPIC study (European Prospective Investigation into Cancer and Nutrition) [Riboli et al., 2002] [29]. The German version of the EPIC questionnaire was kindly provided by the DIFE (Deutsches Institut für Ernährungsforschung, Potsdam, Germany).
- Quality of life Assessment in F 12 short form including twelve questions [Ware et al., 1993; Müller-Nordhorn, 2004] [30] [31].
- A seven-day diet survey including a program that calculates nutritional value (DGE –PC professional, version 5.1) by the German Nutrition Society [32].
- ESS (Epworth-Sleepiness-Scale) [Johns, 1991] [33]

Additionally, questions about origin and family background, religion, employment, education, domestic circumstances, smoking habits, menopause, Mediterranean diet, allergies and sexuality were included. Further, questions were added on usage of mobile phone, sensitivity towards chemical smells, electromagnetic pollution, air and noise pollution.

Health related physical activity

- The objective measurement of physical activity was calculated from a triaxial accelerometer (3D-Activity Sensor Move II, movisens GmbH, Karlsruhe, Germany), which collected raw data at a sampling rate of 64 Hz. The accelerometer was placed on the right hip during seven consecutive days (24h) in a typical working week, but was removed for activities involving water (i.e. showering, swimming). The data were analyzed using software from Movisens GmbH (DataAnalyzer, movisens GmbH, Karlsruhe, Germany), extracting the bouts and non-bouts amount of physical activity energy expenditure in minutes and in metabolic equivalents of task.
- International Physical Activity Questionnaire (IPAQ) was completed after accelerometer recording to display the last seven days [34] [35]. We extended the inventory slightly by adding questions on electrically assisted bicycle and the times in standing or sitting position, as well as sleeping times.
- Questionnaire about regular exercise in different phases of life were recorded in the self-assessed inventory.

Physical Fitness Testing

- Incremental cardiopulmonary exercise testing (CPET) was conducted on a stationary bicycle ergometer (ergo select 200P, ergo line GmbH, Blitz, Germany) including measures of heart rate (12-lead ECG, blood pressure, blood oxygen level (pulsoximeter) and spirometry gases. A gas-exchanger analyzer (Master Screen CPX-Jaeger, VIASYS Healthcare – Respiratory Technologies, LabManager V.5.32.0.) was used for continuous respiratory gas analysis and volume measurements. Before, during and after the CPET the expired air was sampled by using a facemask (Hans Rudolph, Kansas, USA), a volume sensor (Triple-V®) and a gas analyser (Master Screen CPX), which was connected to a semipermeable sampling line (Twin Tube, all products are manufactured by Jaeger, Höchberg, Germany). The exercise protocols were adapted to reach volitional exhaustion after 8–12 min of test

duration, starting with different workloads and increments regarding sex and body mass-range (American College of Sports Medicine, 2013; Pühringer, 2020) [36] [37]. Exclusion criteria were cardiovascular disease, anemia and musculoskeletal disorders.

- Six-meter walking test (6MWT): maximum and habitual walking speed was recorded via a wireless photoelectric beamer (TC, Brower Timing System, Draper, USA).
- Isometric grip force of the right and left hand was measured in a sitting position via a hydraulic hand dynamometer (5030J1, Jamar, Patterson Medical, Dallas, USA).

We used the internet based software EvaSys to collect parts of the data (questionnaires, interview, anthropometry, parts of Ca-scoring, DEXA-scan and carotids parameter). By means of individual codes, the study staff or the participants themselves could fill in data into pre-programmed masks. The data was then stored in the system and was ready for download at any time. Even though the program is internet based, it was incorporated into the internal hospital IT system, protected by the relevant firewall.

2.5. Biobank sample collection

Blood was drawn in sitting position between 7.30 and 10.30 a.m. after at least 10 hours of fasting. The whole blood was collected in special Vacutainer tubes (Greiner Bio-One) for preparation of different types of biological materials.

Blood (EDTA, citrate and heparin), fasting serum and spontaneous urine were centrifuged at 2.000g for 15 minutes in a refrigerated centrifuge (CF5804R, Eppendorf). The supernatant was aliquoted into 2D Data-Matrix coded Screw Cap tubes, that were placed in barcoded Lobarack-96 from Micronic for long time storage at -80°C. The tubes were closed with pierceable TPE Capcluster using electric Capper (Micronic). The barcodes on the tubes and racks were scanned using Traxer Code Reader (Micronic). Information about the type of biological material and location in the freezers was managed using Track-it sample management (Micronic) and LabCollector (AgileBio) softwares.

We collected 24 aliquots of fasting serum, 24 aliquots of fasting plasma EDTA, 8 aliquots of fasting citrate plasma, four aliquots of fasting heparin plasma, 8 aliquots of urine, 12 ml whole EDTA blood, two aliquots of buffy coat and approximately 50gr of stool from each participant. All biological materials are stored at -80°C in Ultra-Low Temperature Freezers from Thermo Fischer Scientific.

2.6. Quality control

During the course of the study, several measures of quality control were implemented. In the first phase of the study, all data manually entered in EvaSys was checked for accuracy. With rising numbers of participants and data sets, only randomly selected data of single participants were checked in detail. The first major quality control was conducted after recruitment of 6,000 subjects. Here, data was checked for plausibility via determination of threshold values. Data that exceeded defined thresholds were compared to raw-data. Additionally, duplicate observations were deleted and missing values were completed if possible. Of all the values (blood pressure and anthropometry parameters) of the 307 participants that

were randomly checked for mistakes, 0.54 % were found to be faulty. In the next and for now last phase of quality control, the program R was used to check for internally inconsistent answers (e.g. medication without known diseases or differences in self-report and interview) [38]. In case of doubt, data was excluded.

Results

Due to inclusion criteria within single examinations, measurements that had to be excluded during quality control and different examination programs, the number of valid observations varies between examinations (Table 1).

3.1: Table 1: List of examinations, the respective program and sample size

Investigation	Program	Sample size
Body height	basic	10050
Body weight	basic	10050
Abdominal circumference	basic	10027
Bioelectrical impedance analysis	extended	2387
Dexa-Scan	extended	1595
Blood pressure	basic	10041
Electrocardiography	basic	10055
Ankle-brachial pressure index	extended	2423
24 h blood pressure	extended	1291
Coronary Artery Calcium Score	extended	1750
Pulmonary function	extended	1812
Liver stiffness measurement	extended	754
5-point OGTT (with insulin)	extended	2151
Medical & family history, medication	basic	9987
ODQ-D	basic	9476
WOMAC	basic	9476
Austrian Social Insurance Inventory	basic	9476
US carotid artery	basic	9968
Salzburg Dementia Prediction Test	basic	7096
Questions on psychological disorders*	basic	9390
BDI	basic	9476
BIS-15	basic	9476
Accelerometry	extended	1605
IPAQ	extended	1324
Questions on exercise **	basic	9476
CPET	extended	1416
Walking Test	extended	1057
Hand Grip Test	extended	1055

AUDIT	basic	9476
EPIC Inventory	basic	8191
QoL F-12	basic	9476
Seven day diet survey	extended	1208
ESS	basic	9476
Further inventories on lifestyle ***	basic	9476
Questions on allergies	basic	8666
Inventory on Mediterranean diet	basic	9231

* includes: questions on major depressive disorder, bulimia and anorexia nervosa, generalized anxiety disorder, manic and hypomanic episodes, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, substance and alcohol abuse.

** regular exercise in different phases of life recorded in the self-assessed inventory.

*** includes: questions on origin and family background, religion, employment, education, domestic circumstances, smoking habits, menopause, Mediterranean diet, allergies and sexuality were included. Further, questions were added on usage of mobile phone, sensitivity towards chemical smells, electromagnetic pollution, air and noise pollution.

OGTT: Oral glucose tolerance test

ODQ-D: Oswestry Low Back Pain Disability

WOMAC: Western Ontario and McMaster Osteoarthritis Index

US: Ultra sound

BDI: Beck Depression Inventory

BIS: Barrat Impulsiveness Scale

IPAQ: International Physical Activity Questionnaire

CPET: Cardiopulmonary exercise testing

AUDIT: Alcohol Use Disorders Identification Test

EPIC: European Prospective Investigation into Cancer and Nutrition

QoL: Quality of Life

3.2. Demographic characteristics of the cohort

The gender distribution in the study cohort shows a balanced plotting between women (51.6%) and men (48.4%), while in the population of the country of Salzburg and whole Austria show a distribution of 51.6% and 50.7% women respectively. The study cohort differs in age distribution from the two reference populations: Due to the study design participants between 40 and 44 years are underrepresented, while participants between 50 and 59 are overrepresented (Fig. 2). Compared to the Salzburg and Austrian population, our cohort is composed slightly of more individuals with Austrian citizenship and no migration background (Fig. 3).

Figure 4 shows an overrepresentation of individuals with higher education level and underrepresentation of individuals with lower education levels in the study cohort compared to the reference groups. Educational level was categorized according to the International Standard Classification of Education (ISCED) [39]. Consequently, more study participants are working as employees and fewer as workers compared to Salzburg and Austrian inhabitants (Fig. 5).

The Salzburg and Austrian population are much more likely to live in rurally urbanized regions, while the greatest part of our cohort is living in densely and intermediately urbanized regions (Fig. 6). Due to this divergence, the parameters education, employment and migration background were additionally investigated with regard to three urbanization degrees, exploring possible relations. There is no difference of trends between the data of employment type and education degree split up in the three urbanization groups (fig. S1 and S2) and all groups put together (Figs. 4 and 5). For details, see supplementary material. In the comparison of the data regarding migration background, the distribution of study participants with first and second generation migration and without migration background living in a rural area approaches the data of the reference groups. The distribution in the study cohort stays constant through out the urbanization degrees, the ones of the reference groups vary with increasing percentage of people without migration background in rural areas compared to urban regions (see supplementary material).

3.3 Life style: Exercise and Smoking

Figure 7 shows a smaller proportion of people who smoke in the study cohort compared to the Austrian and Salzburg population, who additionally conduct more moderate and intense exercise in minutes per week than the study participants (Fig. 8).

3.4 Data on health parameters in the cohort

Table 2: Distribution of anthropometric data, lipid metabolism, glucose metabolism, kidney function and blood pressure in the study cohort, split up into women and men. The 5th and 95th percentile, first and third quartile and median and mean, as well as the standard deviation of data are displayed.

	Sex	N	Five-Number Summary					Two-Number Summary		
			5th Percentile	First Quartile	Median	Third Quartile	95th Percentile	Mean	Standard Deviation	
Age (years)	Total	10043	43	50	55	62	69	56	8	
	Women	5177	44	49	55	61	69	55	8	
	Men	4866	43	50	56	62	69	56	8	
Anthropometric Data	Abdominal Circumference (cm)	Total	10008	73	84	93	102	116	93	13
		Women	5162	71	79	87	96	112	88	13
		Men	4846	82	91	98	105	119	99	11
	BMI (kg/m ²)	Total	10031	20	23	26	29	35	26	5
		Women	5172	19	22	25	28	35	26	5
		Men	4859	22	24	27	29	35	27	4
Lipid Metabolism	Total Cholesterol (mg/dL)	Total	9963	150	184	209	234	276	211	39
		Women	5134	156	188	212	238	280	214	38
		Men	4829	145	180	206	231	271	206	39
	LDL-Cholesterol (mg/dL)	Total	9921	84	116	140	165	204	141	37
		Women	5119	85	114	138	163	204	140	36
		Men	4802	84	117	141	166	204	142	37
	HDL-Cholesterol (mg/dL)	Total	9923	38	50	61	74	96	63	18
		Women	5120	45	58	69	82	102	71	18
		Men	4803	35	45	54	64	82	55	15
	Triglycerides (mg/dL)	Total	9964	49	72	97	137	239	116	80
		Women	5134	47	66	88	121	197	101	62
		Men	4830	54	80	110	157	282	133	93
Lipoprotein(a) (mg/dL)	Total	8594	3	8	18	58	211	51	72	
	Women	4489	3	9	18	62	214	52	73	
	Men	4105	3	8	17	55	207	49	70	
Apolipoprotein B (mg/dL)	Total	9963	70	90	106	124	153	108	25	
	Women	5134	69	88	103	121	149	105	25	
	Men	4829	72	93	110	127	156	111	26	
Glucose Metabolism	HbA1c (%)	Total	9614	5.0	5.3	5.4	5.6	6.2	5.5	0.5
		Women	4924	5.0	5.2	5.4	5.6	6.0	5.5	0.4
		Men	4690	5.0	5.3	5.4	5.7	6.4	5.5	0.6
	Glucose (mg/dL)	Total	9966	79	87	93	100	121	96	17
		Women	5134	78	85	90	97	113	92	14
		Men	4832	82	90	96	104	129	100	19
Insulin (mIU/L)	Total	9254	3.4	5.5	8.0	11.7	23.0	10.0	8.0	
	Women	4804	3.3	5.2	7.3	10.4	19.4	8.9	7.2	
	Men	4450	3.7	6.1	8.8	13.4	25.7	11.1	8.5	
HOMA-IR	Total	9249	0.73	1.23	1.84	2.85	6.28	2.49	2.61	
	Women	4803	0.68	1.12	1.64	2.46	5.01	2.14	2.42	
	Men	4446	0.81	1.41	2.10	3.37	7.46	2.87	2.75	
Kidney Function	Creatinine (mg/dL)	Total	9969	0.62	0.74	0.85	0.96	1.14	0.86	0.18
		Women	5135	0.59	0.68	0.76	0.84	0.96	0.77	0.12
		Men	4834	0.74	0.86	0.95	1.04	1.20	0.96	0.18
eGFR (mL/min/1.73m ²)	Total	9949	60	72	81	91	108	82	16	
	Women	5128	59	71	79	89	107	81	15	
	Men	4821	62	74	83	92	109	84	16	
Blood Pressure	Systolic (mmHg)	Total	10011	105	118	128	139	161	130	17
		Women	5160	103	114	124	136	160	126	18
		Men	4851	111	122	131	142	163	133	16
Diastolic (mmHg)	Total	10012	66	75	81	88	99	82	10	
	Women	5160	65	72	78	85	96	79	10	
	Men	4852	70	79	85	91	101	85	9	

BMI: Body Mass Index, LDL: Low-density Lipid, HDL: High-density Lipid, HOMA-IR: Homeostasis Model Assessment for Insulin Resistance, eGFR: epidermal Growth Factor Receptor.

Follow Up

The first follow up phase of the study started in autumn 2020 and is planned to be finished by 2025. All participants are invited again, approximately 5–7 years after their first visit. The main investigations contain the basic program with additional three parameters: girth of waste, thigh and upper arm. The participants who received extended investigations in the first recruitment phase, will additionally have a magnetoencephalography (MEG), brain magnet resonance imaging (MRI), cognitive testing, echocardiography and ultrasound of abdominal aorta and femoral arteries. The aim is on the one hand to detect clinical events like acute coronary syndrome or stroke, on the other hand to adapt investigations and research questions to the individual subjects. To this end, separate projects and applications will be

designed. Further follow up studies will be conducted accordingly; ideally, the cohort will be followed until the end of the life of each individual participant.

Discussion

During the course of the *Paracelsus 10,000* study, 10,062 participants were recruited and examined. We collected data on physical and mental health, including fitness parameters, lifestyle factors and socioeconomic parameters with a focus on risk factors for cardiovascular and cerebrovascular disease. A biobank with biological samples from study participants was established for future analysis of biomarkers and for use in multi-omic studies.

To get some insight into our study cohort and similarities as well as differences between the study cohort, the Salzburg and Austrian population, we compared characteristics of our study participants with data acquired by the national statistics-institute Statistik Austria [6]. While there is a rather representative distribution of gender, our study population has a higher proportion of participants aged from 50 to 64 years. We intentionally selected participants in this age range as we assume that health status and lifestyle undergo substantial changes in this period of life. A study showed that favorable lifestyle changes in this age span may prevent early death [40]. Our study cohort is less engaged in physical activity compared to the reference group, with respect to intense and moderate exercise (including fast or uphill walking and walking while carrying items). This difference might be explained, at least in part, by differences in the collection of data. Compared to the Salzburg and Austrian population, Austrian citizens are slightly overrepresented in our study cohort, going along with a higher level of education and a greater proportion of white-collar and a lower proportion of blue-collar workers. It has to be mentioned that the questionnaires on lifestyle were issued in German (official and national language in Austria) and not all non-native speakers could be assisted in completing the inventories. Hence, subjects with migration background might have been underrepresented in the dataset acquired by the inventories due to the fact, that they were not able to complete it reliably because of language barriers. This might have influenced also other presented parameters. As most of our participants were recruited from the city of Salzburg, participants living in rural areas were underrepresented in the study cohort as compared to the county of Salzburg and whole Austria. Yet, according to our data, this does not explain the shifted distribution of employment type and education, as white-collar workers and people with higher education are overrepresented in all three urbanization groups. Hence, the discussed characteristics of our cohort seem to be stable throughout urbanization degrees. A fraction of the cohort lives in the countryside, potentially disclosing interesting correlations between urbanization and mental as well as physiological health, lifestyle and living situation. Adding genetic analyses will increase our ability to answer important research questions, increasing relevance and impact of the Paracelsus 10,000 study.

Besides the known limitations of single investigation methods, there are some further weaknesses to discuss regarding study design. As the study was conducted over a period of seven years, changes in background factors (e.g. health policy) might have affected the data, although this is not very likely, since such changes did not occur to a relevant extent in Austria within this time period. The recruitment of all

participants was completed before the first policies regarding the Covid-19 pandemic were implemented in Austria. Hence, collected data like lifestyle, mental health etc. were not directly influenced by consequences of the pandemic. Devices were not changed during this first phase. The inventories we used to collect data about lifestyle, nutrition and exercise were extensive in length and effortful for the participants. This might have decreased motivation of some participants and reliability of collected data. Furthermore, a certain extent of inaccuracy has to be expected due to a general subjectivity of self-reported questionnaires, language problems, lack of motivation and fidelity. Even though the invited people were selected randomly, a certain bias in study population is inevitable. Approximately one sixth of the invited people participated in the study, probably excluding to some extent individuals with a lower degree of health consciousness. Additionally, people suffering from severe diseases might be underrepresented due to logistic reasons and physiological or psychological barriers.

With the provided resources, it was not possible for us to focus on the representativeness of our study cohort. This would require more detailed reference data and further statistical analysis, which would have gone beyond the scope of this manuscript. Yet, answering the question of representativeness of the cohort might be an interesting future project.

Results of the quality control revealed only a small number of missing values and incorrect data, emphasizing the high quality of the study implementation and validity of the collected data. Due to the sample size, the largely randomized study population provides a high variety regarding their health condition, socio economic status and life style factors. Hence, data collection was successful for meeting the studies requirement enabling us in further steps to conduct weighting and high quality analyses. This might be due to a high level of standardization of investigations, conscientious training of staff and background knowledge from different scientific fields including sports science, biology and psychology.

It is of high relevance to further develop and adapt preventive strategies in health care including lifestyle modification. Results of the *Paracelsus 10,000* study might contribute to achieving these goals by providing new insight into the health status of Salzburg inhabitants in an epidemiological setting and into the interaction between genetic and environmental factors for development of common diseases. The follow up period of the study has already started and will give exciting insight into the health development of our cohort during the years to come.

Declarations

Financial Support:

The study was financially supported the Land Salzburg, the Salzburger Landeskliniken (SALK, the Health Care Provider of the University Hospitals Landeskrankenhaus and Christian Doppler Klinik), the Paracelsus Medical University, Salzburg and by unrestricted grants of several pharmaceutical companies (Bayer, AstraZeneca, Sanofi-Aventis, Boehringer-Ingelheim).

Acknowledgement:

The authors thank all contributors of the study, particularly: Stefanie Drach, Johann Sellner, Slaven Pikija, Igor Kedenko, Josef Lang, Alexandra Jarosch, Markus Andress, Katja Vierling, Martin Pühringer, Michael Jordan, Marc Müller, James Anthony and all staff who supported the study during the course of the seven years.

Conflict of interest:

The authors declare that there is no conflict of interest.

Author contribution:

Study initiation: Paulweber, Iglseder, Trinka, Haschke-Becher, Studnicka, Ladurner, Sungler, Fartacek

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Data collection: Frey, Raphaelis, Langthaler, Gostner, Martinz, Kedenko,

Conceptualization: Frey, Raphaelis, Langthaler, Ring-Dimitriou, Paulweber, Iglseder, Trinka

Writing: Frey, Raphaelis, Langthaler

Revision: Ring-Dimitriou, Paulweber, Iglseder, Trinka, Haschke-Becher, Studnicka, Aigner, Kedenko, Bathke

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Figures

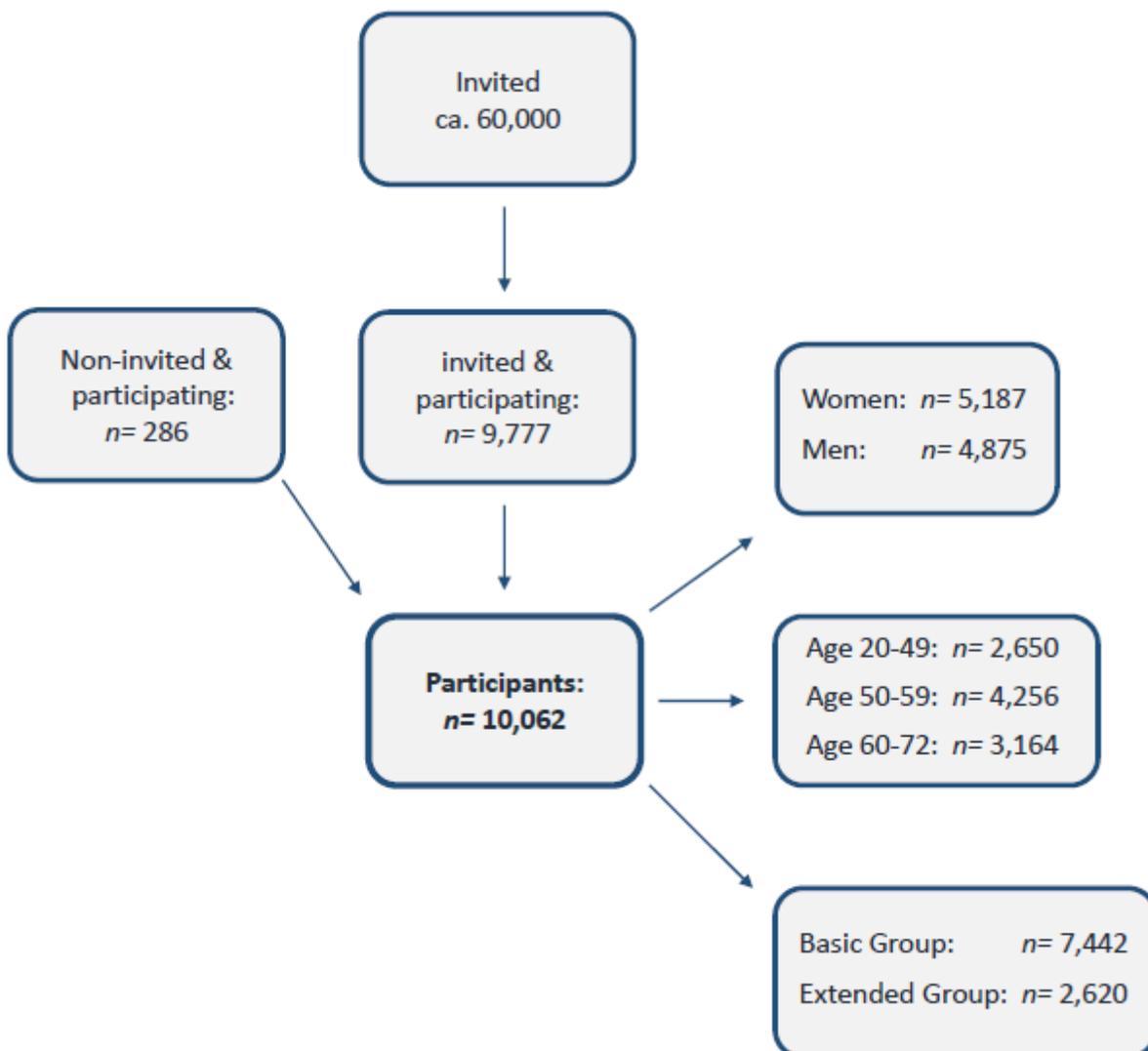


Figure 1

Return rate of invited people and study program, sex and age groups of participants.

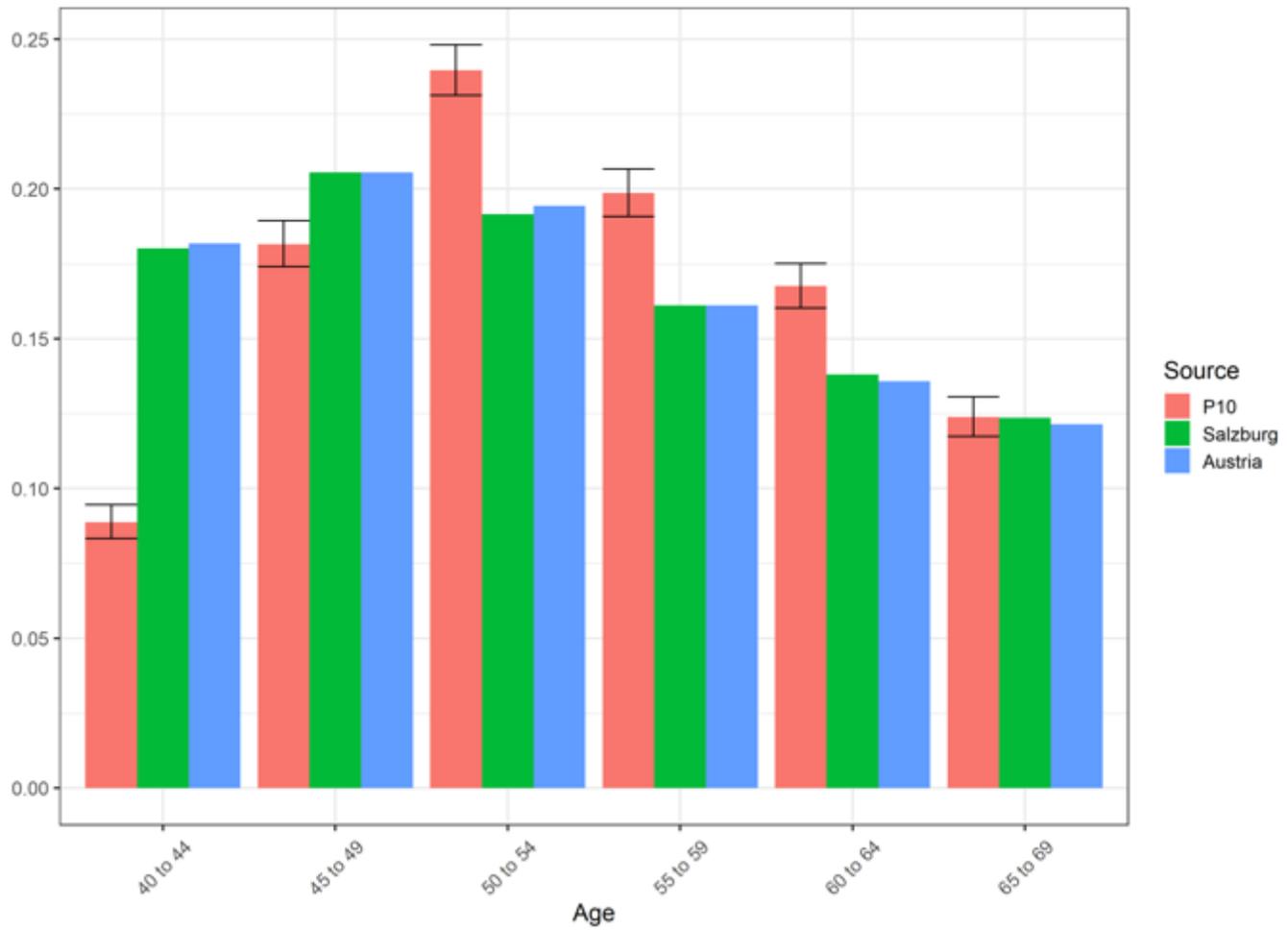


Figure 2

Age distribution from 40 to 69 years of the Paracelsus 10,000 cohort (P10), Salzburg population and Austrian population.

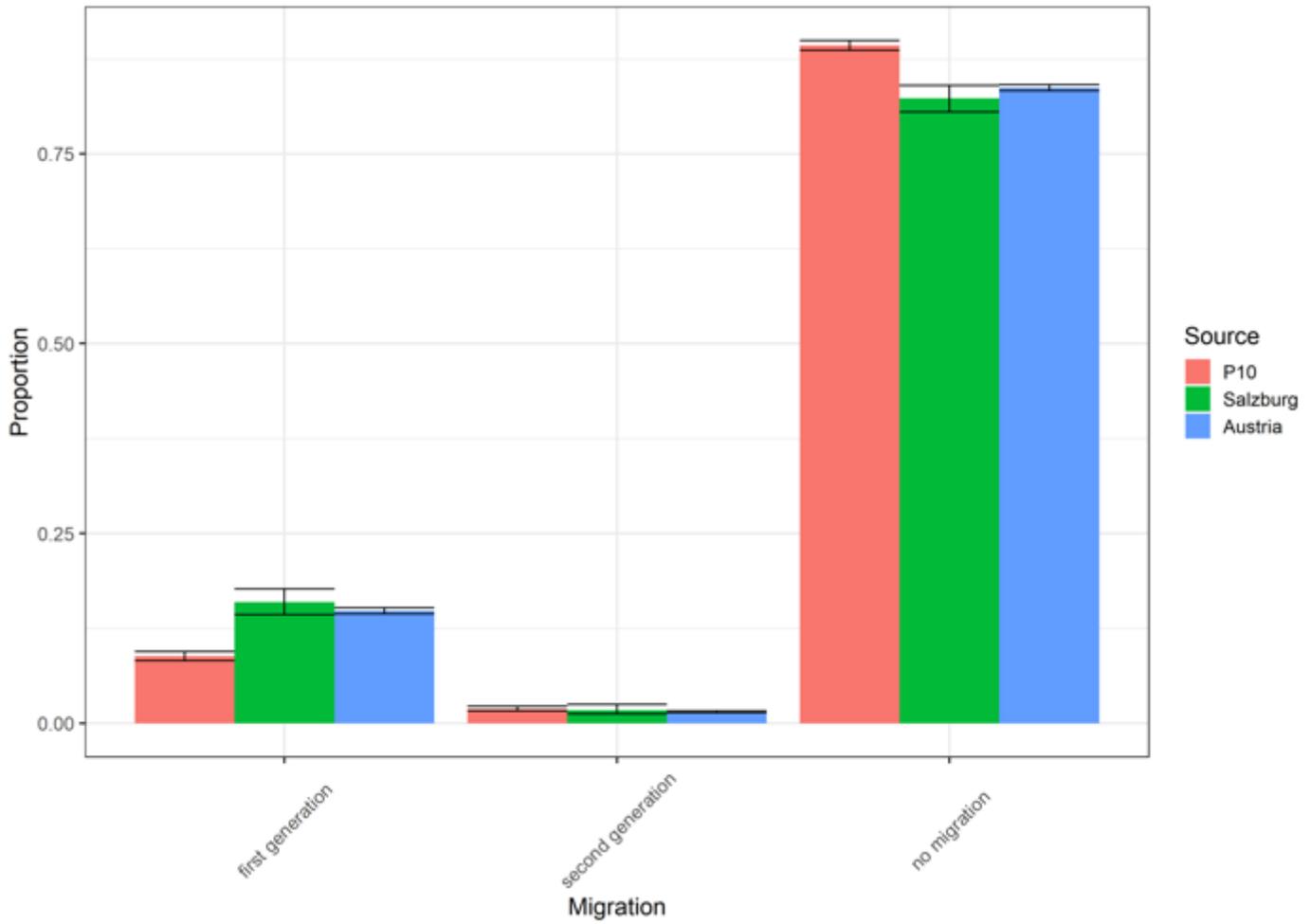


Figure 3

Migration background of the Paracelsus 10,000 cohort (P10), Salzburg population and Austrian population.

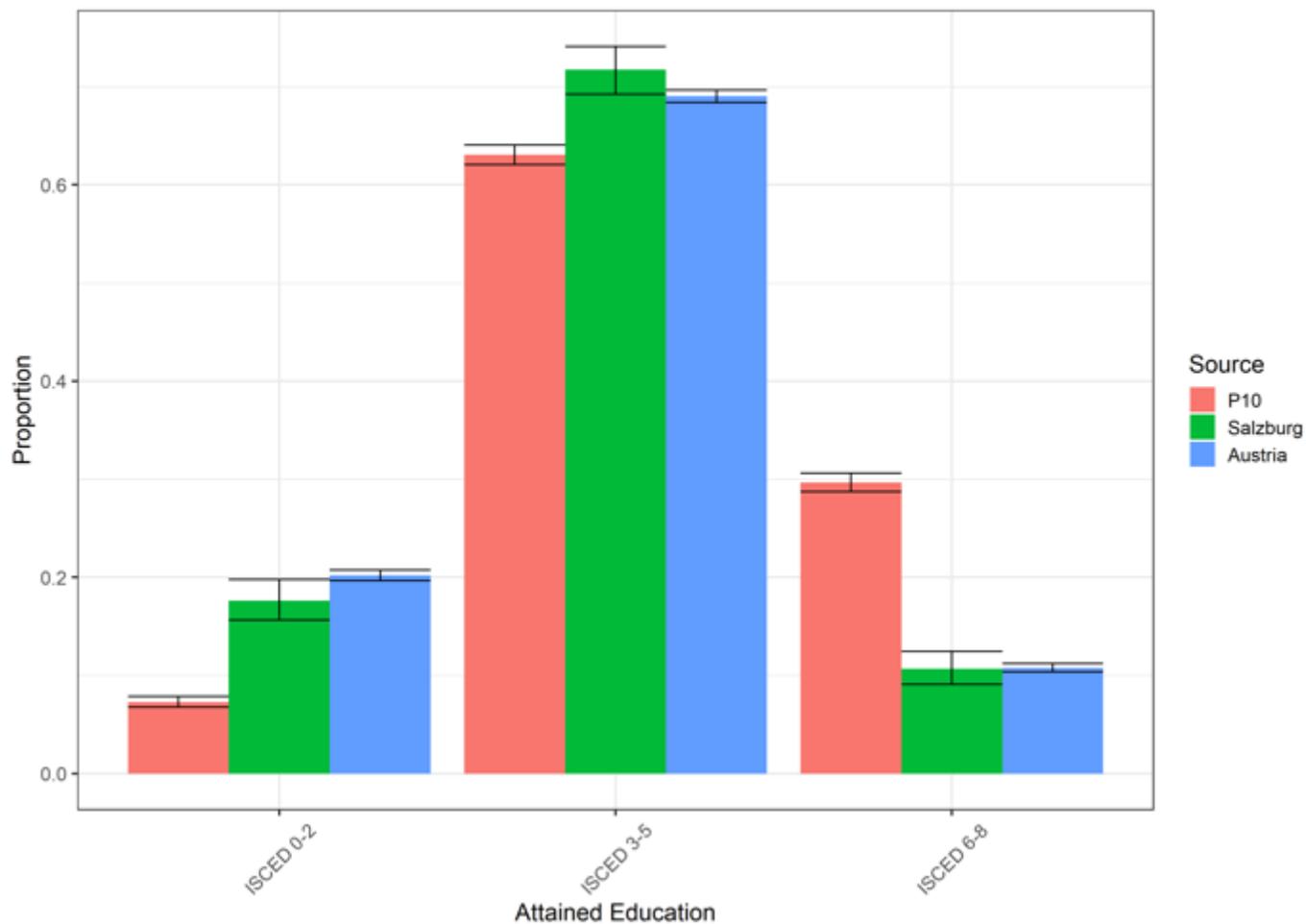


Figure 4

Distribution of education in the Paracelsus 10,000 cohort (P10), the Salzburg population and the Austrian population. ISCED= International Standard Classification of Education.

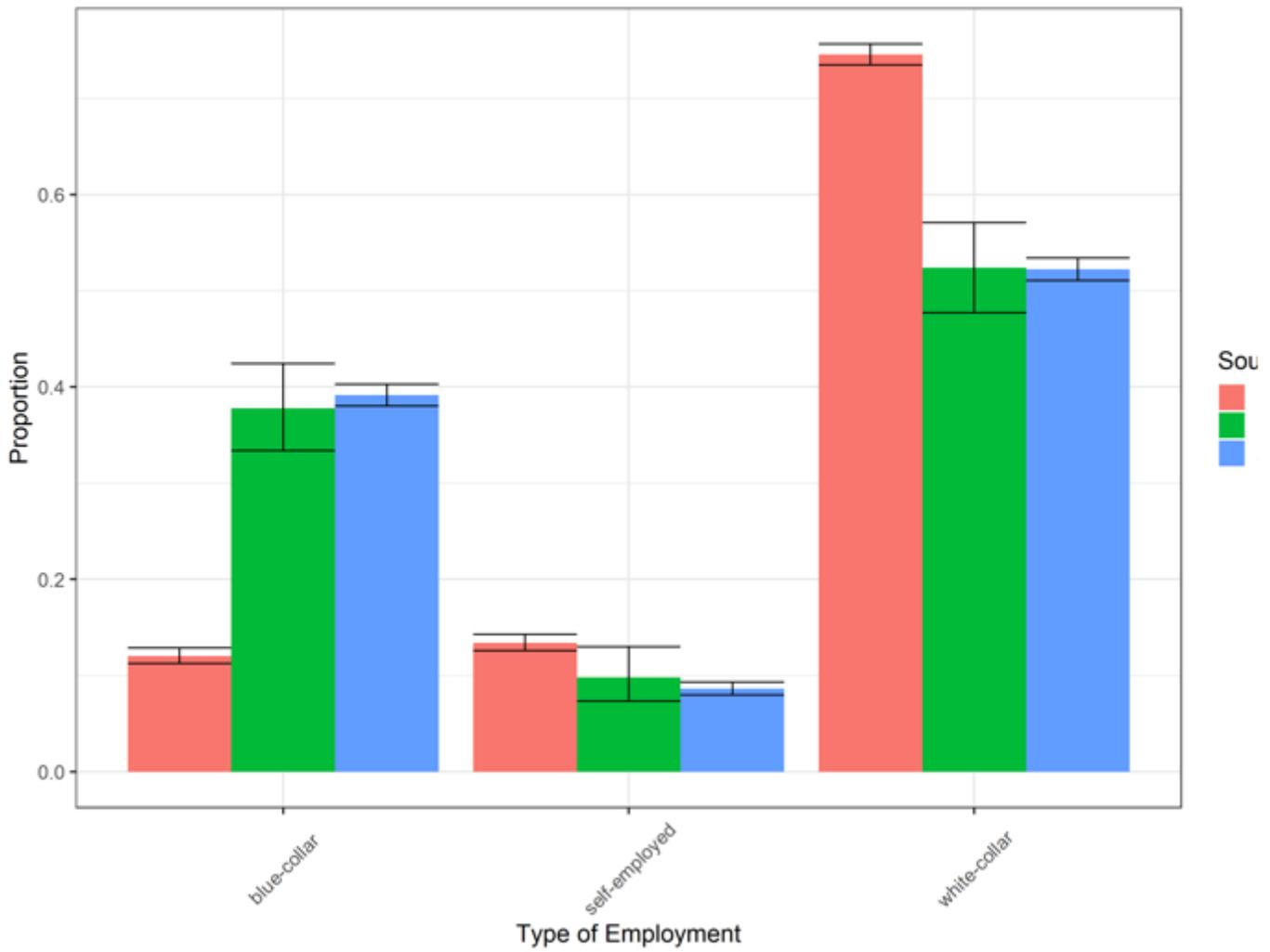


Figure 5

Distribution of employment in the Paracelsus 10,000 cohort (P10), the Salzburg population and the Austrian population.

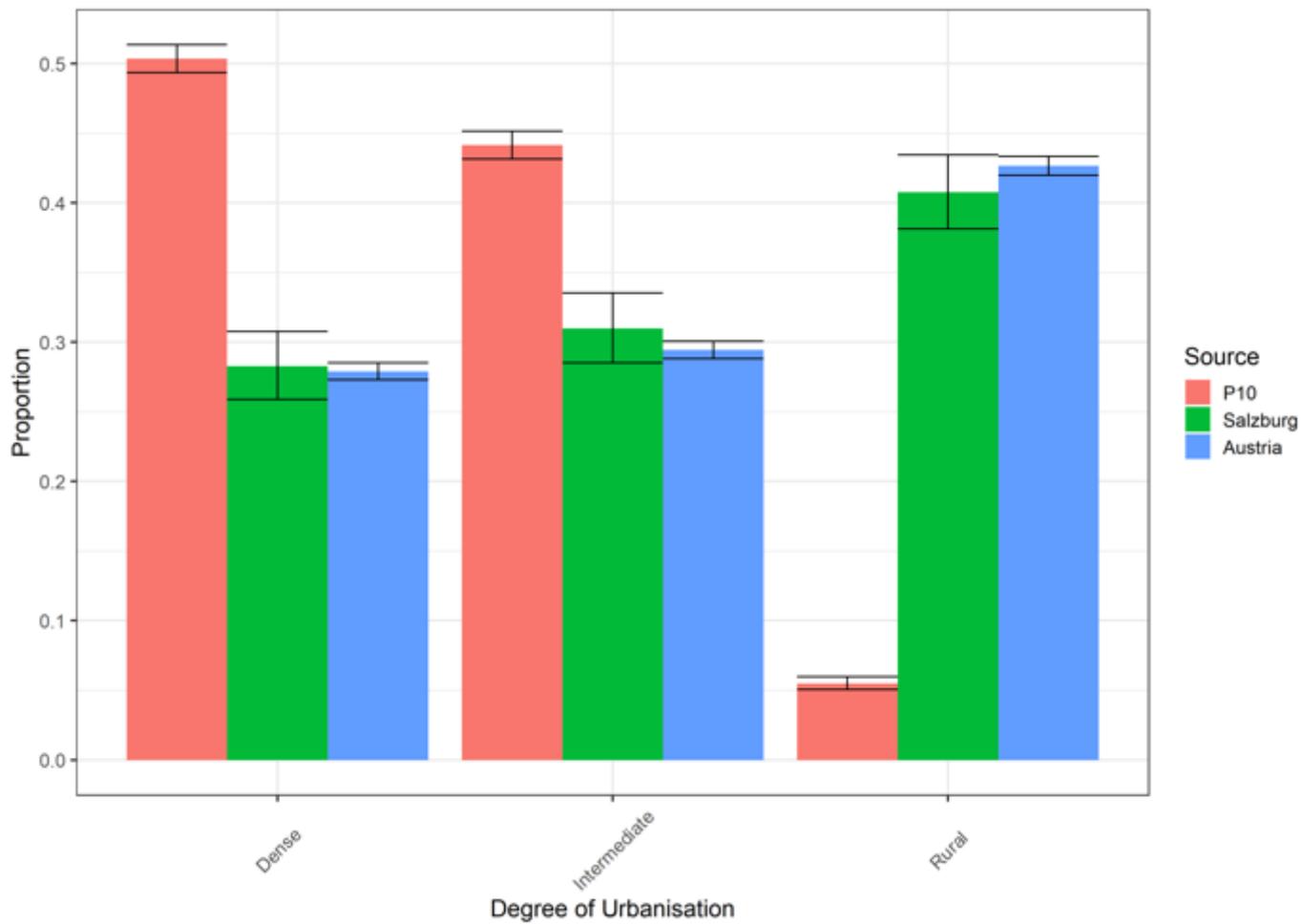


Figure 6

Distribution of the Paracelsus 10,000 cohort (P10), Salzburg population and Austrian population regarding degree of urbanization.

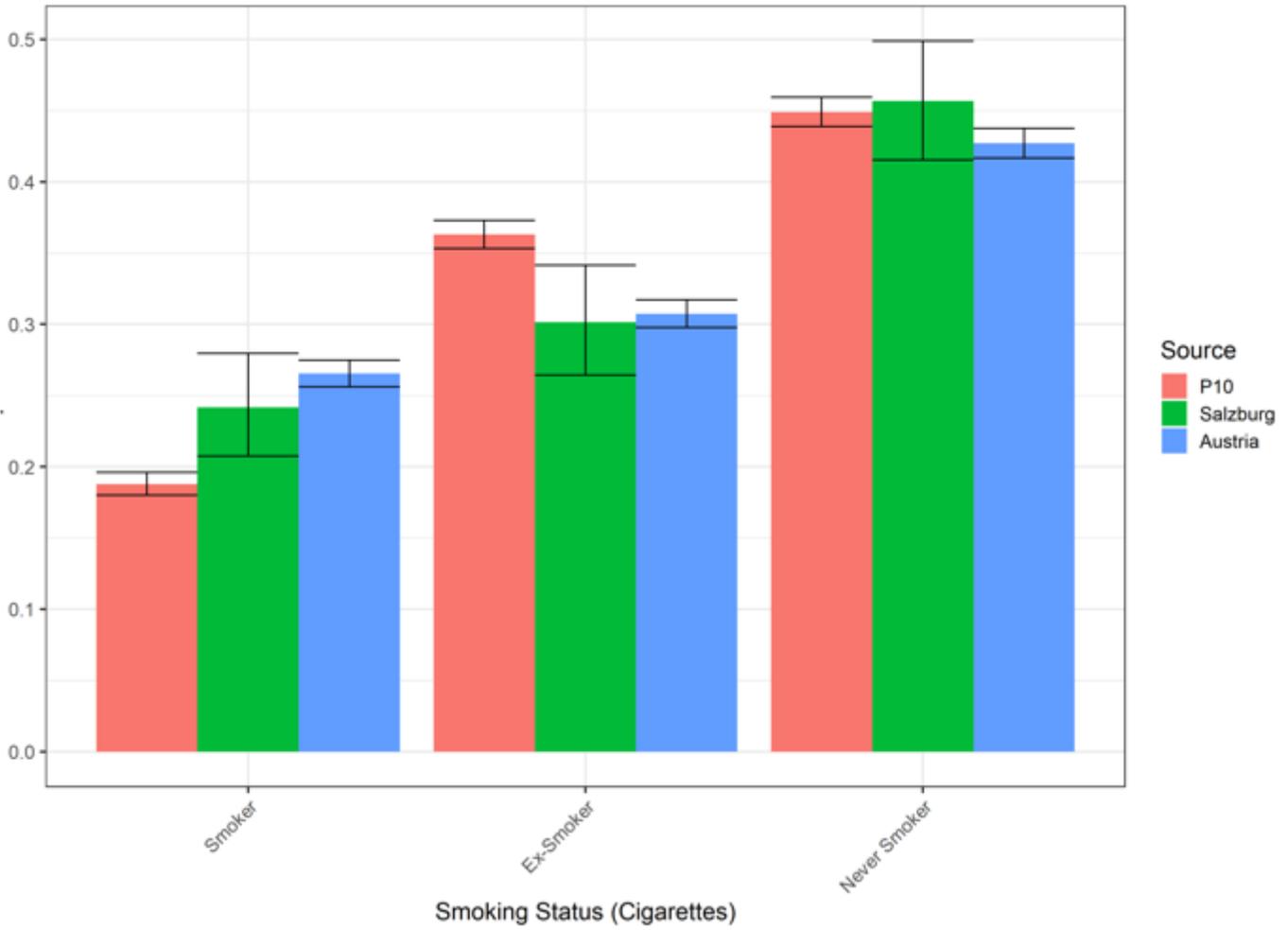


Figure 7

Smoking habits in the Paracelsus 10,000 cohort (P10) and the Austrian population.

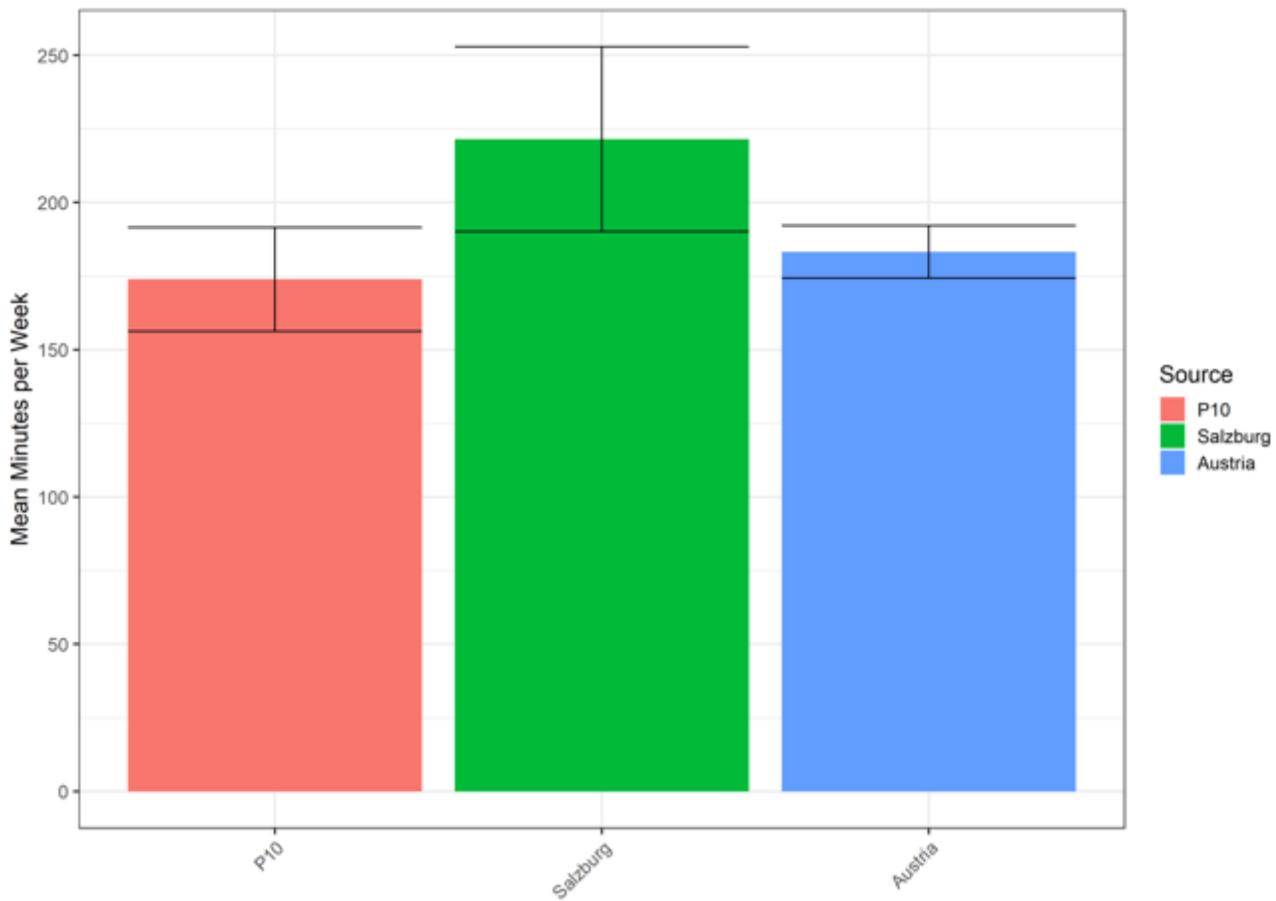


Figure 8

Moderate and intense exercise in the Paracelsus 10,000 cohort (P10) and the Austrian population.

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