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Section: International comparison of health determinants

Follow-up of the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA 2) 1991–2003: methods and characterization of participants

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SAPALDIA Basel is part of Ethics I and II

Ethics

Ethical approval for the study was given by the Overall Regional Ethics Commission for Clinical Medicine (Swiss Academy of Medical Sciences) and each centres' regional ethics committee.

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Summary

Objectives: The Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) was designed to investigate the health effects from long-term exposure to air pollution.
Methods: The health assessment at recruitment (1991) and at the first reassessment (2001–3) consisted of an interview about respiratory health, occupational and other exposures, spirometry, a methacholine bronchial challenge test, end-expiratory carbon monoxide (CO) measurement and measurement for atopy. A bio bank for DNA and blood markers was established. Heart rate variability was measured using a 24-hour ECG (Holter) in a random sample of participants aged 50 years and older. Concentrations of nitrogen dioxide (NO_2), sulphur dioxide (SO_2), ozone (O_3) and particulates in ambient air have been monitored in all study areas since 1991. Residential histories collected over the 11 year follow-up period coupled with GIS modelling will provide individual long-term air pollutant exposure estimates.
Results: Of 9651 participants examined in 1991, 8715 could be traced for the cohort study and 283 died. Basic information about health status was obtained for 8047 individuals (86 % of alive persons), 6528 individuals (70 %) agreed to the health examination and 5973 subjects (62 %) completed the entire protocol. Non-participants in the reassessment were on average younger than participants and more likely to have been smokers and to have reported respiratory symptoms in the first assessment. Average weight had increased by 5.5 kg in 11 years and 28 % of smokers in 1991 had quit by the time of the reassessment.

Keywords: **Cohort study – Longitudinal study – Adults – Chronic disease – Air pollution.**

The most powerful approach for studying long-term effects from ambient air pollution on health is the long-term prospective follow-up of well-defined population-based cohorts with well-characterized air pollution exposure information (European Science Foundation 1998). There are currently only five cohort studies in adults, with published results, that address the long-term impact of air pollution (Abbey et al. 1999; Dockery et al. 1993; Finkelstein et al. 2004; Hoek et al. 2002; Pope et al. 2002; 1995). All studies but one are based in the US and three of them (Dockery et al. 1993; Hoek et al. 2002; Pope et al. 2002), have only published findings related to mortality. The relation of long-term exposure to air pollution with respiratory and cardiovascular health and morbidity has yet to be measured in a large prospective cohort study in Europe. The large European Community Respiratory Health Survey (ECRHS) designed to measure natural history and risk factors for respiratory diseases (particularly asthma and allergy) across Europe has recently included air pollution exposure assessment in its protocol (Burney et al. 1994; Hazenkamp-von Arx et al. 2004). However, the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) is the only prospective cohort study of respiratory and cardiovascular health in adults in Europe with detailed individual residential exposure histories as a key element of the assessment of effects from long-term exposure to air pollution.

The SAPALDIA cohort is a random population sample of 9561 adults recruited and examined in 1991 (for detailed description of methods see (Martin et al. 1997)). There were extensive health examinations, a detailed assessment of personal risk factors, assessment of average exposure to the pollutants O_3, NO_2, SO_2 and PM_{10} in ambient air and assessment of individual exposure to NO_2. Findings from the study showed effects from passive smoking exposure on respiratory symptoms (Leuenberger et al. 1994) and from air pollutant on lung function and symptoms (Ackermann-Liebrich et al. 1997; Künzli et al. 2000; Schindler et al. 1998; 2001; Zemp et al. 1999) and from occupational exposure and atopy on bronchial responsiveness (Leuenberger et al. 2000; Schwartz et al. 2002). References values from lung function (Brändli et al. 1996; 2000) and the prevalence of atopy and allergic symptoms have been described (Strupler et al. 1997; Wüthrich et al. 1995; 1996; 1999).

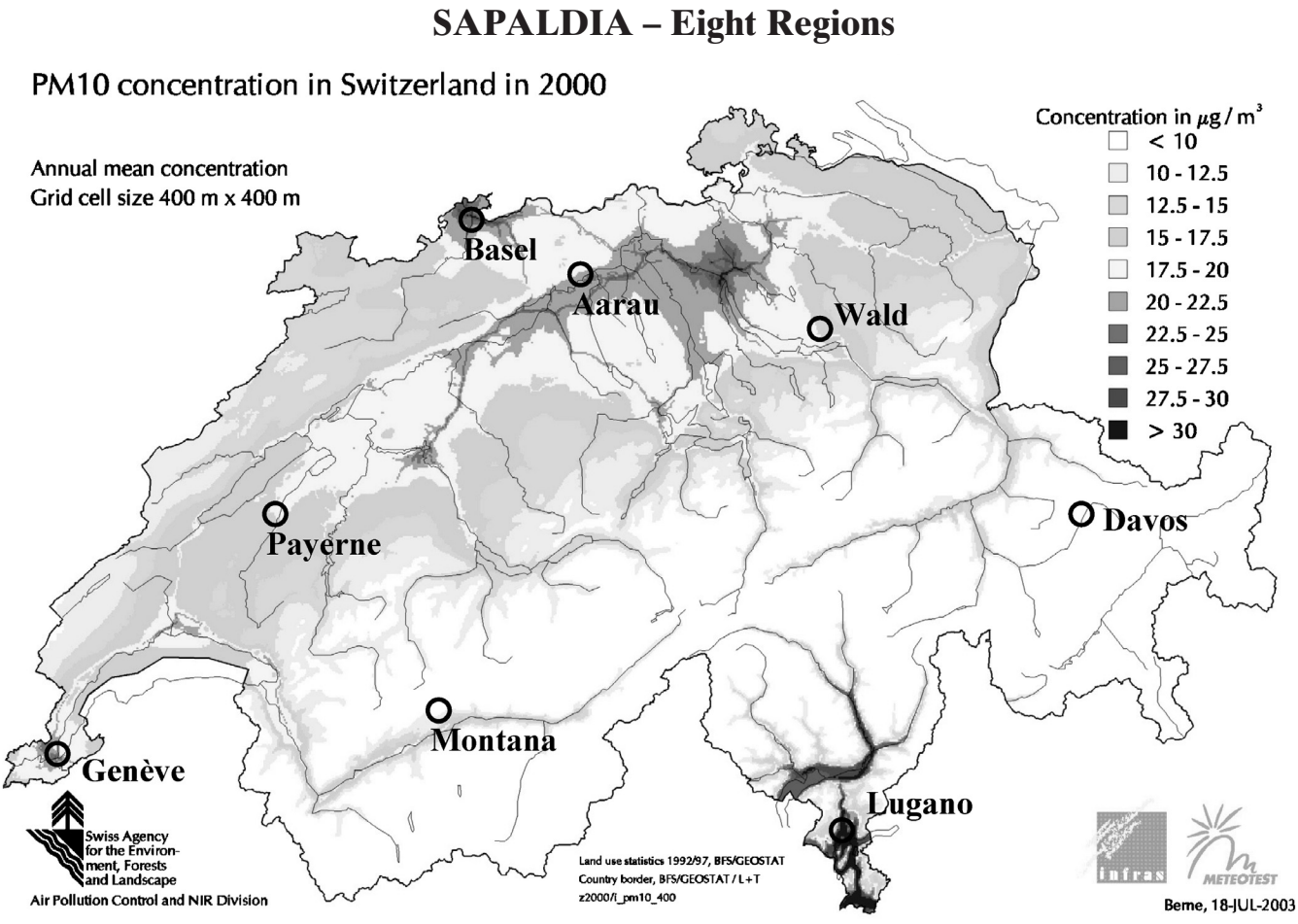
Monitoring of air pollutants, meteorology and pollen has been conducted in all study areas since 1991. Regular mailings to the 9651 original participants has ensured that changes in residential address and deaths (n = 283) amongst participants since 1991 have been updated. Of the surviving 9368 participants, 93 % (8715) could be traced between 2001–2003. This paper describes the health examinations, the bio bank, the environmental monitoring, and the assessment of air pollution exposure and basic characteristics of the participants in SAPALDIA 2.

Methods

The milestones of the SAPALDIA study (1991–2001)

The eight study areas (Geneva, Basel, Lugano, Aarau, Wald, Payerne, Davos, Montana) were chosen to represent the variety of environmental conditions in respect to geography, climate, degree of urbanisation and air pollution in Switzerland. From the local registries of inhabitants of these areas random population samples of persons aged 18–60 years, who had been residents in the respective area for at least three years, were then drawn (Martin et al. 1997).

Map of Switzerland and of the eight study areas



Health examinations were conducted at the eight local centres over the course of one year in 1991 and repeated in 2002. Detailed description of the 1991 examinations can be found elsewhere (Martin et al. 1997).

Contact with the 9 651 participants of SAPALDIA 1 (including monitoring of mortality) has been facilitated by regular mailings and updates every 1.5 years through the information collected from participants by mail or from local registries of inhabitants. The residential history database was checked at the local registries in all study areas in 1998 and 1999.

Recruitment for the SAPALDIA follow-up (2001–2003)

Extensive efforts were made to contact all original participants of SAPALDIA 1 for the follow-up examination in SAPALDIA 2. A letter of invitation describing the health examinations, was sent to all former participants who could be traced. The letter contained a screening questionnaire (with 13 questions about respiratory symptoms, smoking, date of birth and address) and a prepaid addressed envelope for the return of the response to the local study centre. Up to three letters were sent and up to 12 telephone calls made (at different times during the day including morning, noon, evening and weekends) in an attempt to contact the non-responders. In non-responding subjects without telephone number, SAPALDIA personnel made home visits. If all attempts to make contact failed; the subject was considered to be untraceable (n = 653, 6.8%).

The protocols for SAPALDIA and the European Community Respiratory Health Survey (ECRHS) (Burney et al. 1994) are similar (Tab. 1) and participants from the SAPALDIA Basle centre aged 18–44 in 1991 are also participants in the ECRHS study.

Since ECRHS II was initiated slightly in advance of SAPALDIA 2, examinations at the Basle centre preceded those in other SAPALDIA centres. Examinations in Basle were started in July 2001, and between October 2001 and January 2002 in the other centres (Aarau, Davos, Geneva,

Table 1 Comparison of assessments in SAPALDIA and ECRHS

	SAPALDIA Cross-sectional 1991	SAPALDIA Follow-up 2001–2003	ECRHS Follow-up 2001
Questionnaires			
PC based interview	yes	yes	yes
Paper questionnaires:			
– SF36, quality of life	no	yes	yes
– JuniperAsthma quality of life	no	yes	yes
– Occupational exposure	no	yes	yes
– Women's questionnaire	no	yes	yes (some centres)
Lung parameter assessment			
Spirometry	yes	yes	yes
Bronchochallenge	yes	yes	yes
End-expiratory CO	yes	yes	no
Cardiovascular assessments			
Blood pressure	no	yes	no
Ambulatory ECG	no	yes	no
Assessment of allergy			
Skin prick test	yes	no	no
Blood markers (IgE)	yes	yes	yes
Assessment of genetic factors			
Blood for DNA isolation	no	yes	yes
Assessment of genotypes	no	yes	yes (some centers)
Assessment of other risk factors in blood			
Cardiovascular risk factors	no	yes	no
Hormones in females	no	yes	yes (some centres)

Lugano, Montana, Payerne, Wald). Examinations in all centres were completed by the end of February 2003.

Informed consent

Ethical approval for SAPALDIA 2 was given by the central ethics committee of the Swiss Academy of Medical Sciences and the Cantonal Ethics Committees for each of the eight examination areas. The consent information provided to participants described the health examination including the bronchial challenge, the ambulatory electrocardiogram (ECG) and blood collection. Additionally there was information about data protection and the genetic assessments. Participants were required to give written consent before any part of the health examination was conducted and were provided with written consent information to read and were given the opportunity to ask questions about the examination. Subjects could either give global consent (for all health examinations) or agree to each investigation separately.

Documentation

All study documentation, including questionnaires and protocols, was provided in German, French and Italian because native languages differed between SAPALDIA centres. Documents were usually conceived in German or English and then translated in French and Italian. Translations were cross-checked in simultaneous readings with SAPALDIA research personnel who were native speakers of the respective languages and fluent in at least one of the other languages. This procedure had already been used in 1991 and at that time back-translations were also used for validation. As the majority of questionnaires were already available in the three languages, back-translations were unnecessary in SAPALDIA 2.

Interview administered main questionnaire

The interview was conducted by a trained fieldworker and answers from the participant were entered directly into an Access database on a personal computer. As in SAPALDIA 1, the interview included questions about history of respiratory symptoms, allergic diseases, general health, living and working environment, smoking habits, exposure to traffic, exposure to environmental tobacco smoke and animals. In SAPALDIA 2 the questionnaire was extended with additional questions about chronic diseases, including heart disease, questions about dietary habits (adapted from the Swiss Health Questionnaire (Bundesamt für Statistik 2001/2004), physical activity (derived from the ECRHS II- and the Swiss Health Questionnaire) and sleepiness (derived from the Epworth Sleepiness Scale (Johns 1991)). Present and past medication use was recorded in detail; including type, dose, start date of medication use and duration.

Additional questionnaires administered included the Quality of life (SF36) questionnaire (Ware 1994), the Juniper Asthma quality of life questionnaire (Juniper et al. 1993) (given to the subjects who had answered "yes" to the question: "Have you ever had asthma?") and a women's questionnaire (with questions about menstruation, menopausal status and intake of hormones) (Tab. 1 and 3a). In addition, a card was handed to all pre-menopausal women with the request to send the card back with the date that their next menstrual cycle commenced in order to determine their hormonal status at the time of health examination. A job exposure matrix (Kennedy et al. 2000) was used to assess occupational exposures since SAPALDIA 1. Participants who had worked as cleaners (in a job and at home), nurses, metal workers, solderers, welders and participants who had worked with disinfectants were also asked to complete an occupational questionnaire specific to the occupational activity or exposure. Participants also completed an address/ZIP code table indicating residential location(s) for the period of 1991–2001.

The computer-based interview took on average 45 minutes per participant. If participants were unable or unwilling to come to the examination centre, one of two shorter questionnaires were administered over the telephone. The short questionnaire contained a selection of 64 questions from the main interview about respiratory symptoms and medication, chronic diseases, current occupation, exposure to traffic, active and passive smoking and emergency visits at the hospital. The ultra-short questionnaire comprised 32 questions about respiratory symptoms, medication, current occupation, exposure to traffic, active and passive smoking.

The following definitions based on answers in the main questionnaire are used in Figures 1a and 1b:

Current smoker: Positive answer to the question "Have you ever smoked for as long as a year?" ("yes" means at least 20 packs of cigarettes or 360 grams of tobacco in a lifetime or at least one cigarette per day or one cigar a week for one year).

Chronic cough: Positive answer to the question "Do you usually cough during the day, or at night, on most days for as much as three months each years?" and an answer of ≥ 2 to the question "For how many years have you coughed like this?"

Chronic phlegm: Positive answer to the question "Do you usually bring up phlegm from your chest during the day or at night on most days for as much as three months each years?" and an answer of ≥ 2 to the question "For how many years have you brought up phlegm like this?"

Wheeze: Positive answer to the question "In the last 12 months, have you had wheezing or whistling when you did not have a cold?"

Shortness of breath: Positive answer to the question "Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?"

Chest tightness: Positive answer to the question "In the last 12 months, have you woken up with a feeling of tightness in your chest?"

Blood pressure measurement

Systolic and diastolic blood pressures were measured after the interview and after the participant had sat quietly for at least 10 minutes. Pressures were measured twice with an interval of at least 3 minutes using an automatic OMRON 705 CP (Tokyo, Japan) with the cuff attached to the naked left upper arm.

Collection and fractioning of blood samples

Blood samples were taken from all subjects who had consented to the general blood marker analyses and/or the genetic analyses. 45 ml of blood was collected for blood marker analysis into differently coated 9 ml Monovette tubes (SARSTEDT; Nuembrecht, Germany). EDTA-coated tubes were used for collection of blood, plasma and buffy coat, Lithium-Heparin-coated tubes for plasma collection and non-coated tubes for serum collection. With the exception of one EDTA-coated tube, the samples were centrifuged at room temperature (20 °C, 15 min, 1500 g) using a UNIVERSAL 32 R centrifuge (Hettich AG, Baech, Switzerland). Subsequently the fractioned and EDTA-buffered whole blood samples were aliquoted (300 to 500 µl) into 1ml TPP Cryotubes (Trasadingen, Switzerland) and transferred to –80° C immediately. The blood sample collection and fractioning procedure was performed within a maximum of four hours. If possible, 40 aliquots were prepared per subject, (corresponding to 3 vials of buffy coat, 3 of EDTA-plasma, 4 of EDTA-buffered whole blood, 10 of Li-He-plasma, and 20 vials of serum). For DNA extraction, 7 ml of whole blood was collected in EDTA-coated Monovette tubes, which were stored without previous centrifugation at –80 °C.

Constitution of the blood plasma, serum and DNA banks

The samples extracted from blood were stored in eight SANYO freezers (Applewood, ON, Canada) with a storage volume between 519 (U71V) or 728 litres (U50V) that were connected to emergency back-up systems (including an alarm system and/or CO2 backup). After completion of the

data collection phase in spring 2003, all freezers were transported to one location (University Hospital, Geneva) for sample sorting. The blood bank containing about 250 000 blood aliquots was split into two identical banks. For reasons of security and accessibility the two bio banks are now located in two different centres for long-term storage (University Hospitals of Geneva and Zurich). During the transport, inside freezer temperatures were monitored and did not increase above –60 °C at any time.

The whole blood samples taken for genetic analysis were transferred on dry ice to the laboratory performing the DNA extraction (Departments of Molecular Epidemiology and of Medical Molecular Genetics, University of Zürich). The blood samples were processed manually using the PUREGENE™ DNA Purification Kit (GENTRA Systems, Minneapolis, USA). The observed DNA yields ranged from 7–80 µg of DNA obtained from 1 ml of frozen EDTA-buffered blood.

Quality of genomic DNA was evaluated in terms of DNA degradation visually on 0.8% agarose gel electrophoresis and in terms of purity by performing standard and allele-specific PCR amplification.

Subsequently, DNA working solutions were generated by diluting the DNA with milli-Q-pure water and concentration was adjusted to 10 ng/µl. Barcode-labelled 2 ml tubes with screw-caps (SARSTEDT; Nuembrecht, Germany) were used to store DNA stock and working solutions. DNA working solutions were kept at –20 °C for long-term and 4 °C for short-term storage. In analogy to the blood specimen bank, the DNA stock solutions were transferred for accessibility and security reasons to two locations (Zurich and Geneva).

A computer-based data bank (Excel format) was established, containing an identification code for each participant, coordinates identifying the location of each type of biological sample (serum, both type of plasma, buffy coat, whole blood, and DNA), the number of vials present, DNA extraction remarks, concentration and volume of available DNA stock solution, DNA quality characteristics and the location of the diluted DNA working solution.

Weight and height measurements

The participants were asked to remove all heavy clothes such as shoes, jacket, coat etc. For the height assessment, telescopic scales, model 222, from SECA (Hamburg, Germany) were used. The scale was permanently fixed unto the wall and the participant was required to make contact to the wall with the backside of his head, the upper back, the rear, the lower legs as well as with his heels during the measurement. An electronic scale (T160-T620-T630) from TERRAILLON (Bradford, MA, USA) was used for the weight measurements. Weight was displayed digitally in kilograms to one decimal point. The scales were calibrated with standardised weights at regular intervals. The height scales were checked during quality assessment visits.

Carbon monoxide measurement

In order to validate participants answers to smoking habits end-expiratory carbon monoxide (CO) was measured with EC50 Micro-Smokerlyzer, (BEDFONT, Rochester, UK). Participants were asked to first completely exhale, then to inhale fully, to hold their breath for at least 20 seconds and finally exhale completely through the mouthpiece of the measuring device. CO devices were calibrated approximately every six months.

Spirometry

The same spirometers based on an open system using a mass flow anemometer (Sensormedics model 2200, Yorba Linda, USA), meeting American Thoracic Society (ATS) performance criteria, were used in both SAPALDIA 1 and 2. A quality assessment in 2001 demonstrated that measurement of lung volumes by the eight spirometers were comparable to one another (Kuna-Dibbert et al. 2005). The same spirometry protocol was followed in SAPALDIA 1 and 2 that was identical to the protocol in ECRHS (Künzli et al. 1995). Spirometers were calibrated twice a day using a standardised three litre syringe. Participants performed manoeuvres in a sitting position wearing nose clips. At least three and up to maximal eight forced expiratory lung function manoeuvres were performed in order to obtain a minimum of two acceptable results for for both FEV_1 and FVC and the forced expiratory flows (FEF_{25}, FEF_{50}, $FEF_{25–75}$ and FEF_{75}) were recorded from each manoeuvre. Flow-volume curves and codes indicating compliance with American Thoracic Society criteria were displayed on computer screen as each manoeuvre was performed (American Thoracic Society 1995) to assist the technicians in the selection of acceptable manoeuvres. Spirometry technicians were also required to report problems during the test that could affect quality of trials. Expiratory flow measures were taken from the flow-volume curve with the highest sum of FVC and FEV_1. As in SAPALDIA 1, all spirometry outputs were visually screened by respiratory physicians experienced in lung function testing. There were 370 flow-volume curves from 237 participants excluded because of abnormalities that indicated technical problems during the performance of the manoeuvre (Townsend et al. 2004).

Methacholine bronchial challenge

Non-specific bronchial responsiveness was assessed by bronchial challenge with methacholine chloride in participants able to produce satisfactory spirometry, and who fulfilled health criteria. Participants were excluded if they had had a myocardial infarction in the last 12 months, were taking medication for heart disease, had epilepsy, were pregnant, were lactating and/or were receiving treatment with any beta blockers including eye drops. The protocol followed in SAPALDIA 2 was identical to that in SAPALDIA 1. Methacholine (PROVOCHOLINE®, Methapharm Inc., ON, Canada) was administered by MEFAR aerosol dosimeters (Anandic Medical Systems, Diessenhofen, CH) starting with inhalation of physiological sodium chloride (NaCl) followed by increasing concentrations of methacholine up to a cumulative dose of 2 mg. The dosimeter was triggered automatically at the beginning of the inhalation and the subjects were instructed to hold their breath at full inspiration for four seconds. Between one and two minutes after the end of each inhalation two FEV_1 manoeuvres were performed and the manoeuvre with the highest FEV_1 recorded. The test was stopped when either the cumulative dose of 2 mg had been reached or FEV_1 had fallen by 20% or more compared to the NaC_l baseline value or the participant refused to continue. A bronchodilator (Salbutamol®, 200 µg) was offered to participants who experienced a drop in FEV_1 during the challenge. Seven new Mefar nebulisers were purchased for SAPALDIA 2. All nebulisers were calibrated in 2001 by the manufacturers in Melbourne Australia. Driving pressures from the Mefar dosimeters were checked periodically at the centres using a manometer. All challenge tests were assessed for compliance with the study protocol.

24 hour Holter electrocardiogram (ECG)

Only participants aged 50 and older were eligible for a 24 hour electrocardiogram (ECG) monitoring with a Holter recorder (Aria, Del Mar Medical Systems, Irvine California). Exclusion criteria included having a cardiac pacemaker, having undergone anaesthesia during the previous eight days or having taken anti-arrythmic drugs class I or III or digitalis glycosides within the last 30 days.

The Holter monitor was fitted by placing one of three electrodes (Blue Sensor, Medicotest, Stykke, Denmark) 2 cm to the right of processus xiphoideus, another electrode on the left linea medioclavicularis on the lowest rib and the third electrode was located on the left front axillar line on the lowest rib. During the ambulatory ECG monitoring period, participants completed a location and activity diary derived from a diary previously developed for the EXPOLIS study (Jantunen et al. 1998). The SAPALDIA ECG diary contained fields for recording information on the participants whereabouts (indoor, outdoor etc), levels of activity, caffeine and alcohol use, consumption of tobacco (active and passive) and medication for every 15 minute interval during the monitoring period.

Quality control procedures

Instruction protocols for all methods and parts of the study were prepared in a written form. Fieldworkers participated in a three day training workshop, before the beginning of the study. Each fieldworker was required to test at least 10 volunteers at the centre under supervision before starting to examine participants. Three additional workshops for fieldworkers were held during the data collection period to assure high data quality. In addition, quality control visits to all eight centres were conducted three times during the examination phase. At each visit at least one full examination was observed and possible improvements were discussed with the fieldworkers. Furthermore, compliance with required standardised operating procedures was checked and oral and written feedback provided. Moreover, differences in the quality between fieldworkers and centres in the conduct of spirometry were assessed in detail and reported back to the fieldworkers. The quality control visits also offered a platform for feedback from the local teams about the participation rates and quality of the recorded data received by the central coordinating team. During the data collection period, six SAPALDIA bulletins with information and feedback were distributed to all centres. The bulletins addressed issues relating to data collection and quality and provided additional information about topics that had been raised during workshops and quality control visits.

Environmental data

In each SAPALDIA region, criteria gases (NO_2, SO_2, ozone) and fine particles (PM_{10}, $PM_{2.5}$) have been monitored at central sites. The core of these air pollution measurements have been conducted within the national (NABEL) and cantonal monitoring networks, providing long-term routine data for six of the eight SAPALDIA regions. Measurements initiated by SAPALDIA closed the gaps in the monitoring network (Montana and Wald) and regarding parameters not routinely assessed ($PM_{2.5}$).

Air quality standards for PM_{10} were introduced in Switzerland in 1996 making measurement of PM_{10} mandatory. Measurement of PM_{10} by Harvard impactors was introduced in the SAPALDIA regions already in 1993. The changes in PM_{10} measuring technologies since then have been taken into account for calculating PM_{10} time series between 1991 and 2002. Annual means of PM_{10} before 1997 could be esti-

mated as fraction of total suspended particulates (TSP) (Gehrig & Hofer 1999) in Geneva, Lugano, Basel, Payerne and Davos, while in Wald and Montana Harvard impactor data was converted to the reference method Digitel HiVol sampling (Monn & Krütli 1999). $PM_{2.5}$ has been measured in all SAPALDIA areas since 1999. Personal, indoor and outdoor NO_2 has been measured by SAPALDIA participants in 1992/93 using palmes tubes (Monn et al. 1998) and indoor and outdoor NO_2 again in 2002/03. In addition to air pollutants, meteorological parameters and pollen data have been collected for each SAPALDIA area.

In SAPALDIA 1, exposure assignment relied predominantly on data from a single monitor in each community. Most participants lived within seven kilometers of the local monitoring stations and we had demonstrated that particulate matter, one of our primary indicators of ambient air pollution, is homogeneously distributed within such distances and not much affected by local traffic (Röösli et al. 2000; 2001). Moreover, we have found ambient $PM_{2.5}$ from outdoor sources to be correlated with personal exposure to $PM_{2.5}$ (Oglesby et al. 2000). As indicator of spatially less homogenous traffic-related pollutants, we chose NO_2 as primary candidate, and conducted complementary neighborhood monitoring in SAPALDIA1. The latter showed associations with lung function within areas not observed with PM_{10} (Schindler et al. 1998).

In SAPALDIA 2 the single monitor approach was extended towards individual exposure estimates. The goal is the assignment of individual long-term air pollution exposure to each subject, taking into account changes in residential location during the 11 year follow-up period. Approximately 20% of SAPALDIA 2 participants moved from their original study area in SAPALDIA 1. Therefore, estimates of ambient concentrations of air pollutants from other areas need to be incorporated into exposure estimates. Exposure estimates for SAPALDIA 2 participants will be derived from NO_2, PM_{10} and $PM_{2.5}$ maps resulting from emission-based models using Geographical information system technology (GIS) which have been validated by monitoring data from fixed sites. The model for NO_2 will be further validated and, if necessary, adjusted using outdoor NO_2 palm tubes measurements made by sub-samples of SAPALDIA 1 and SAPALDIA 2 participants at their homes and GIS-data on traffic-related parameters such as distance to street. The resulting models of ambient pollutant levels over the follow-up period will then be linked to the residential locations of SAPALDIA participants thereby providing individual exposure estimates.

Results

Participation in examinations

In 1991, 9651 subjects participated in SAPALDIA 1. By 2001, 283 (2.9%) participants had died (194 men, 89 women), 653 (6.8%) had moved abroad or were not traceable by March 2003. Therefore, 8715 subjects (93% of the survivors of the original cohort) could be contacted (Tab. 2). Of these 8715 subjects, 8047 (92% or 86% of survivors) completed at least one questionnaire (screening questionnaire, main interview questionnaire or short versions of the main interview questionnaire). Participants who provided more information than the screening questionnaire were classified as responders and as having participated in SAPALDIA 2 (N=7 680=88% of traceable and 82% of living participants in 2001) (Tab. 3a).

There were 6 528 SAPALDIA 2 participants who performed spirometry and of these 6 222 provided spirometry data that met quality criteria. For the methacholine challenge test, 167 participants (2.6%) had to be excluded on the basis of an FEV1 less than 70% of predicted or less than 1.5L. Other participants were excluded on the basis of having had a myocardial infarction within the last three months, receiving medication for heart disease, pregnancy, lactation, treatment with beta blockers (13.3%), no consent for testing (7.3%), and other reasons which included doubts about health status of the participant, unsatisfactory manoeuvres, technical problems and loss of data (8.2%). Of the 4 655 participants who had a bronchial challenge; data from 4211 (90.5%) participants met quality criteria.

We collected blood samples of 6 327 participants who agreed to blood marker analysis and extracted DNA from blood of 6215 participants who agreed to genetic testing. Of the random sample of older participants invited to participate in the measurement of ECG; 1 860 provided an ECG for a continuous period of more than 20 hours. Table 3 a and b give an overview on participation in examinations and the numbers of questionnaires of different types. There were 6 207 subjects, representing 66% of the survivors of the original cohort, who completed the entire protocol (interview, spirometry and blood sample); and valid data is available for 5973 (62%).

Description of participants in SAPALDIA 1 and 2

To test the hypothesis that participation was associated with health-related behaviours (e.g. smoking) and health status (e.g. lung function and symptoms), we compared participants in both SAPALDIA 1 and 2 to participants who only participated in SAPALDIA 1 using data collected at SAPALDIA 1. Figures 1a and 1 b show the prevalence of

Table 2 SAPALDIA participants in 1991 and traceable and untraceable subjects in 2001–2003, Switzerland

Centre of examination	Subjects in SAPALDIA cross-sectional part991	Subjects who died	Subjects who moved abroad or address is untraceable	Potential participants in follow-up 2001–2003		Questionnaire information (= participants)		Spirometry		Broncho-challenge		Blood samples	
	N	N	N	N	%	N	%[1)]	N	%[2)]	N	%[3)]	N	%[2)]
Basel	1491	59	121	1311	87.9	1192	83.2	861	72.2	591	68.6	806	67.6
Wald	1518	29	36	1453	95.7	1399	94.0	1186	84.8	918	77.4	1178	84.2
Davos	745	16	59	670	89.9	637	87.4	534	83.8	452	84.6	513	80.5
Lugano	1310	35	120	1155	88.2	1140	89.4	908	79.6	589	64.9	870	76.3
Montana	794	25	45	724	91.2	694	90.2	613	88.3	477	77.8	610	87.9
Payerne	1495	54	124	1317	88.1	1168	81.1	882	75.5	611	69.3	856	73.3
Aarau	1299	39	37	1223	94.1	1080	85.7	986	91.3	723	73.3	981	90.8
Geneva	999	27	117	855	85.6	736	75.7	558	75.8	294	52.7	531	72.1
TOTAL	**9651**	284	659	**8708**	90.2	**8047**	85.9	**6528**	81.1	**4655**	71.3	**6345**	78.8

[1)] Percentage of surviving subjects
[2)] Percentage of participants
[3)] Percentage of spirometry

Table 3a Questionnaires submitted to the 2001–2003 follow-up of SAPALDIA, Switzerland

	Nb. of subjects
Screening questionnaire	367
Ultrashort questionnaire	**193**
Short questionnaire	**907**
Interview	**6573**
Spirometry or blood with only a screening questionnaire	7
Total	**8047**
Self-administered questionnaires:	
Women's questionnaire	3153
Menstruation Card	1021
Asthma quality of life	298
SF 36	5703
Epworth sleepiness scale	6092
Occupation list	6045
Medication list	3404
Cardio time activity diary and holter	1807
Residence list	5713

never and current smokers and selected respiratory symptoms in participants in SAPALDIA 1 and SAPALDIA 2. An adjusted means procedure was utilised to show the prevalence in SAPALDIA 2 adjusted for smoking and symptom characteristics of all participants in SAPALDIA 1 (STATA Corporation, Texas 77845, Special Edition release 8.2). Overall, participants in both SAPALDIA 1 and 2 had slightly less symptoms in 1991 and were more likely to be non-smokers than those who did not participate in the follow-up. As expected there was a small increase in prevalence of some respiratory symptoms, specially wheeze and classic phlegm, and a considerable proportion (28%) of smokers had quit smoking.

Tables A1 and A2 in the appendix show the distribution of BMI by age groups and sex. There was a considerable increase of weight in this population between assessments (the mean weight increase was 5.5 kg/person). The mean

Table 3b Completeness of tests

	total number of participants	Given blood	ECG	Blood & ECG
Interview[1)]	7673	6345	1813	1763
Interview + spirometry[2)]	6218	5975[4)]	1693	1649
Interview + spirometry + methacholine challenge[3)]	4113	3998	1054	1035

[1)] Interview includes subjects who answered either the long, short or ultra-short interview questionnaires and excludes subjects who only answered the screening questionnaire
[2)] Spirometry that met good quality criteria
[3)] Methacholine challenge that met good quality criteria
[4)] "Complete" examinations meeting quality criteria

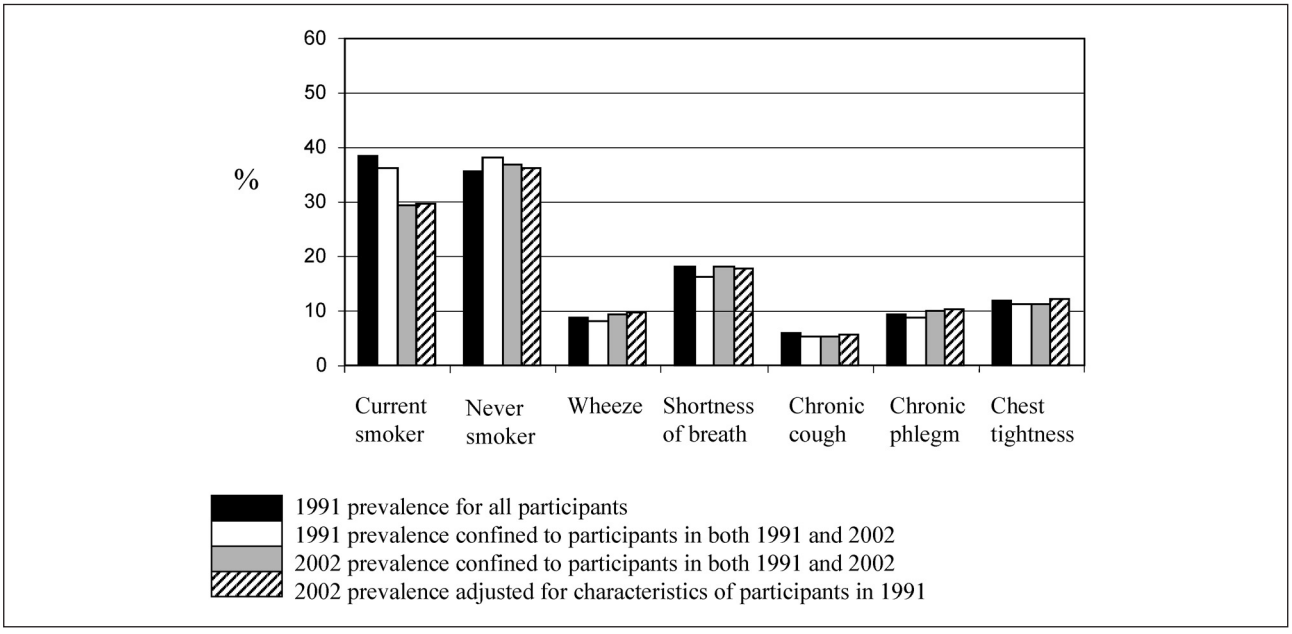


Figure 1a Participation in SAPALDIA in men by smoking status and respiratory symptoms (for definitions, see Methods section), Switzerland, 1991 and 2002

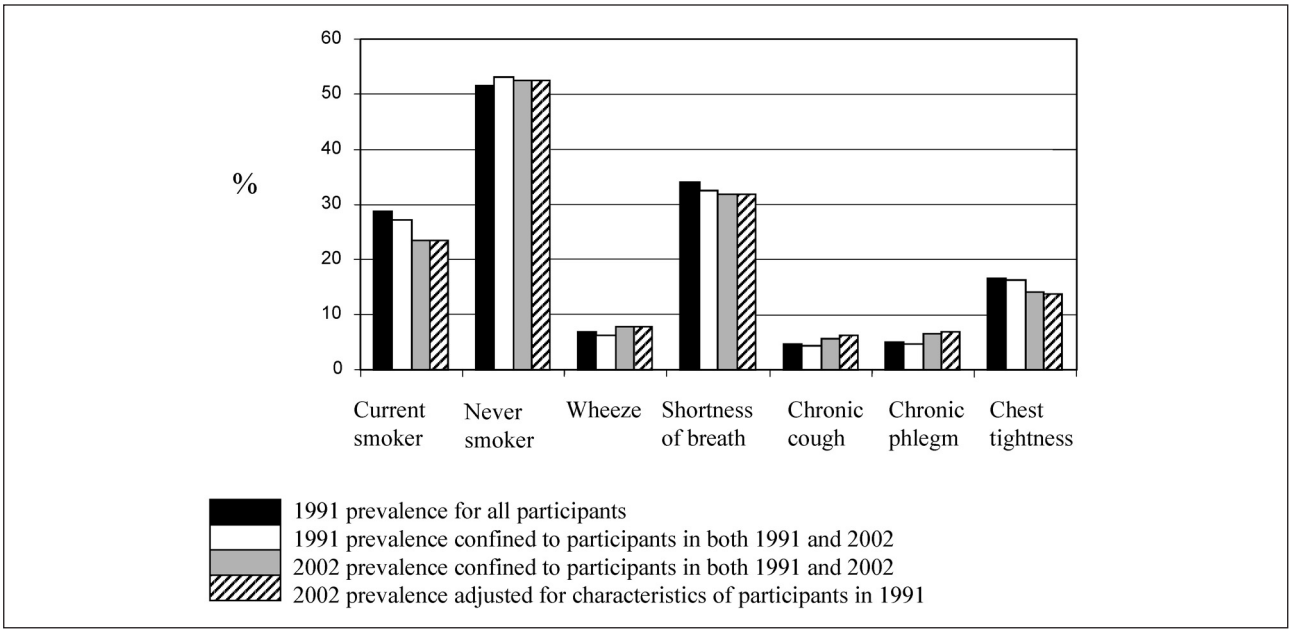
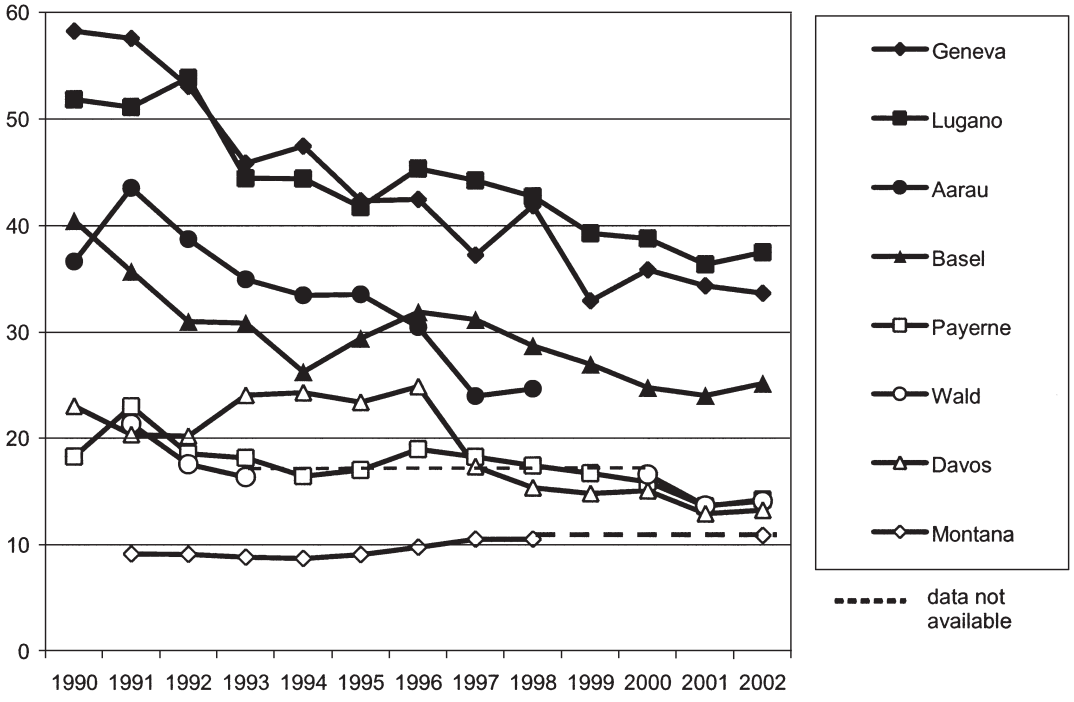


Figure 1b Participation in SAPALDIA in women by smoking status and respiratory symptoms (for definitions, see Methods section), Switzerland, 1991 and 2002

weight gain was highest in younger men and decreased in both sexes after 55. The Tables in the Appendix also show the distribution of lung function (measured by forced expiratory volume in one second and forced vital capacity), the prevalence of the selected respiratory symptoms as well as the prevalence of current smoking and amounts of cigarettes smoked per day.

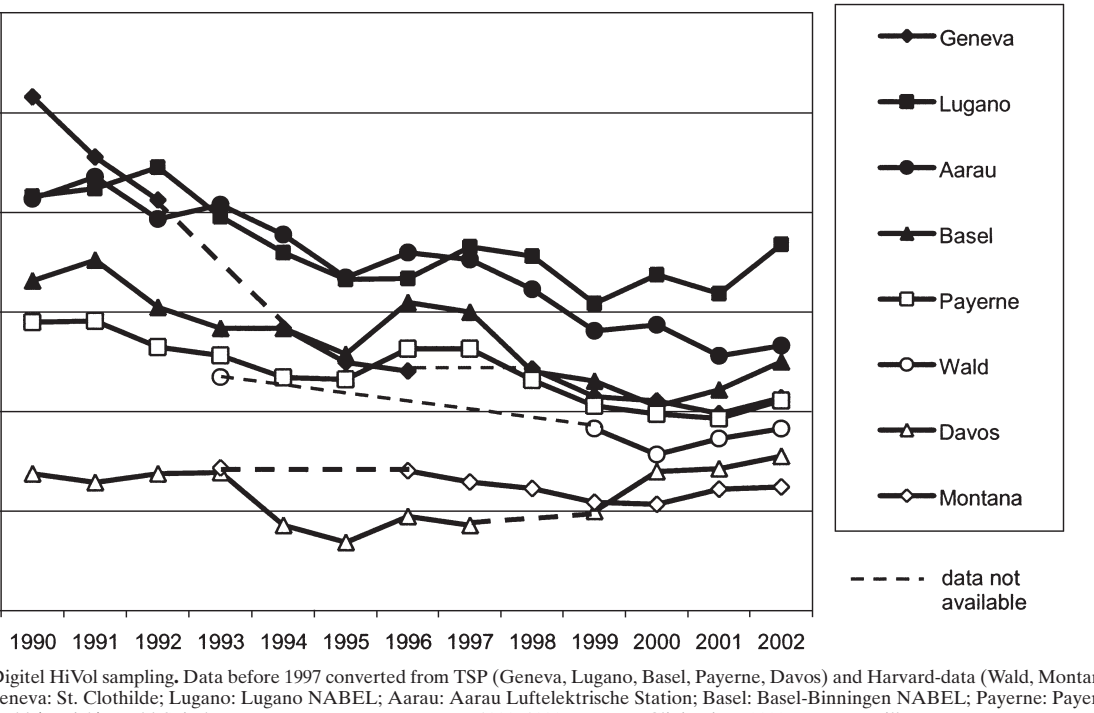
Development of air pollutants between SAPALDIA 1 and 2

Ambient concentrations of NO_2 and PM_{10} have decreased in most SAPALDIA areas since 1991 (Fig. 2a and 2b). In most areas the strong decrease of the early 1990s was partially levelled out by increasing levels due to meteorological factors in the years just before SAPALDIA 2, particularly for PM_{10}. The strongest absolute decline of NO_2 was observed in the



Method: Chemilumineszenz
Stations: Geneva: St. Clothilde; Lugano: Lugano NABEL; Aarau: Aarau Luftelektrische Station; Basel: Basel-Binningen NABEL; Payerne: Payerne NABEL; Wald (Zurich): Wald-Spital; Davos: Davos-Matta; Montana: 1990–1998 Montana-Clinic, since 2002 Montana-Village.

Figure 2a 12-year course of NO2 [µg/m³] in the SAPALDIA Regions, Switzerland



Methods: Digitel HiVol sampling**.** Data before 1997 converted from TSP (Geneva, Lugano, Basel, Payerne, Davos) and Harvard-data (Wald, Montana)
Stations: Geneva: St. Clothilde; Lugano: Lugano NABEL; Aarau: Aarau Luftelektrische Station; Basel: Basel-Binningen NABEL; Payerne: Payerne NABEL; Wald (Zurich): Wald-Spital; Davos: Davos-Matta; Montana: 1990–1998 Montana-Clinic, since 2002 Montana-Village.

Figure 2b 12-year course of PM10 [µg/m³] in the SAPALDIA Regions, Switzerland

two areas with the highest 1991 baseline levels, Geneva and Lugano, while the alpine area Montana exhibited on a low level a slight increase. The absolute and relative decline of PM_{10} in most areas was less pronounced compared to NO_2. Differences between the areas remain, especially for NO_2, though the air pollution exposure contrast between areas has been reduced since SAPALDIA 1.

Discussion

Despite a demanding study protocol, a high participation rate was achieved in the SAPALDIA follow-up. Comparison of characteristics at SAPALDIA 1 showed some differences between SAPALDIA 2 participants and non-participants, but most differences were small and are unlikely to bias the main analyses of the study.

The most striking feature was the high proportion of smokers in 1991 who had quit by 2002. In view of the lower participation of smokers in 2001 this raises the question of selected recruitment; those who gave up might have been more motivated to participate in a health examination. The Swiss national Health Survey (Bundesamt für Statistik 2001/2004) shows an increase in the proportion of former smokers with age (18% in men aged 35–44 to 42% in the 64–75 age group, with a stable proportion in each age group between 1992 and 2002).

The SAPALDIA cohort gained weight in the past 11 years. The average increase in body mass index (BMI) in young men was 3.7 kg/m^2, on average subjects weighed 5.5 kg [SE 0.08] more than in 2002 compared to 1991. The distribution of BMI in the SAPALDIA population compares favourably to the MONICA Augsburg population (Gasse et al. 2002) and the Chianti population (Bartali et al. 2002), within both sexes and across all age groups, although women in Innsbruck seem to be slimmer (Ulmer et al. 2001). The BMI reported by Schilling (Schilling et al. 2001) for Swiss employees seems comparable to the distribution for women in our study, but as their results relate to the years 1996–98 one might speculate that the distribution of BMI in their population might also have been higher in 2002.

As for the amount of cigarettes smoked, an interesting comparison with the Innsbruck Women's Health Study (Ulmer et al. 2001) is possible. While the proportion of smokers is considerably higher in Innsbruck (40% in the youngest age group and 35% in women aged 40–59) the mean number of cigarettes smoked per day is higher in the Swiss female population. Since these results from SAPALDIA 2 are consistent with data from other Swiss surveys and prevalence estimates for symptoms from SAPALDIA 2 did not change much after adjustment for differential non-participation we conclude that the SAPALDIA population sample reflects the distribution of risk factors for non communicable diseases in an average Swiss population.

SAPALDIA was designed to investigate the effects of air pollutants on respiratory health (including lung function, development of symptoms and diseases) in a random sample of the adult population of Switzerland. Given the high participation rate in the SAPALDIA follow-up we have sufficient power to test the association of respiratory, allergic and cardiovascular outcomes with air pollution parameters over the course of 11 years. In SAPALDIA 2, the urban centres Basel and Geneva had lower participation rates. We therefore expect that the trend towards healthier more educated participants is amplified in these cities, which might result in an under-estimation of the effects of ambient air pollution, since they might live in less polluted places. However since we are able to look at differences within individuals as well as by area sampling effects by area become less important. Throughout the 11 year follow-up period air quality has been continuously monitored and a steady decline in most pollutant levels has been observed. The individual long term exposure assignment (based on personal residential history and GIS modelling of air pollutant concentrations) will increase power to detect the effects of ambient air pollution at different levels of cumulative exposure (Künzli & Tager 2000). These improvements in individual exposure assignment should counterbalance the relative loss in power due to the steady decrease in pollution levels which ultimately reduces the exposure contrast in the SAPALDIA study.

The DNA collected in the follow-up will enable us to address emerging questions about the interaction of environmental and genetic factors in important diseases and might help to detect especially sensitive subgroups.

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Zusammenfassung

Die Schweizer SAPALDIA-Kohortenstudie (SAPALDIA 2) 1991–2003: Methoden und Teilnehmendencharakteristika

Fragestellung: Die Schweizer Kohortenstudie Luftverschmutzung und Atemwegserkrankungen bei Erwachsenen (SAPALDIA) untersucht die gesundheitlichen Auswirkungen der Langzeitbelastung durch Luftschadstoffe in der Bevölkerung.

Methoden: 1991 und 2002 wurden ein Interview zur respiratorischen Gesundheit und deren Risikofaktoren, eine Spirometrie, ein bronchialer Reagibilitätstest mit Methacholin, eine endexpiratorische Kohlenmonoxidmessung und Tests zur allergischen Sensibilisierung durchgeführt. Für SAPALDIA 2 wurde eine Biobank mit Blut-, Serum-, Plasma- und DNA-Proben eingerichtet. Eine Stichprobe der über 50-jährigen Teilnehmenden erhielt ein 24-Stunden EKG (Holter). Luftschadstoffkonzentrationen von Stickstoffdioxid (NO_2), Schwefeldioxid (SO_2), Ozon (O_3) und Schwebstaub (PM_{10}) wurden in allen acht Studiengebieten seit 1991 gemessen. Die seit SAPALDIA 1 erfassten Adressgeschichten und auf GIS-Technologie beruhenden Schadstoffverteilungsdaten für NO_2 und PM_{10} werden die Schätzung der individuellen Langzeitbelastung jedes SAPALDIA-Teilnehmenden ermöglichen.

Ergebnisse: Von der ursprünglichen Kohorte von 9 651 Teilnehmern in 1991 waren 283 verstorben und Adressen konnten von 8715 aufgefunden werden. Basisinformationen zum Gesundheitszustand von 8047 Personen (86 % aller lebenden Personen) wurden erfasst, 6528 (70 %) nahmen an der Untersuchung teil und für 5973 (62 %) liegen vollständige SAPALDIA2-Untersuchungen vor. Nichtteilnehmende waren im Durchschnitt jünger, weniger gut ausgebildet, eher Raucher und hatten eher respiratorische Symptome. Die untersuchten Personen haben in den letzten 11 Jahren durchschnittlich 5,5 kg Körpergewicht zugelegt, 28 % der RaucherInnen haben aufgehört zu rauchen.

Résumé

Etude de cohorte SAPALDIA (Etude Suisse sur la pollution atmosphérique et les maladies respiratoires chez l'adulte): méthodes et caractéristiques des participants

Objectifs: L'étude SAPALDIA a pour objectif de mesurer les effets sur la santé d'une exposition à long terme aux polluants atmosphériques dans la population adulte.

Méthodes: Les participants ont été interrogés en 1991 et en 2002 sur leur état de santé respiratoire et ses facteurs de risque. Ils ont passé les examens suivants: spirométrie, test de la réactivité bronchique et de l'atopie, mesure du CO en fin d'expiration. Une banque biologique a été créée. Un ECG (Holter) a été pratiqué auprès d'un échantillon de participants âgés de plus de 50 ans. Les concentrations des polluants atmosphériques (dioxyde d'azote (NO_2), dioxyde de soufre (SO_2), ozone, particules fines (PM_{10})) ont été mesurées dans huit régions de Suisse depuis 1991. L'exposition individuelle sur 11 ans sera déterminée à partir des adresses, de la distribution de NO_2 et PM_{10} et les modèles GIS.

Résultats: Sur les 9 651 participants examinés en 1991, 283 sont décédés, 87 15 ont été localisés, 8047 ont donné des informations sur leur état de santé (86 % des personnes en vie), 6528 participants (70 %) ont accepté d'effectuer l'examen de santé et 5 973 (62 %) ont réalisé entièrement le protocole. Les non participants étaient en moyenne plus jeunes, moins éduqués, plus fréquemment fumeurs et souffraient plus fréquemment de symptômes respiratoires. Les personnes examinées ont pris en moyenne 5,5 kg de poids en 11 ans. 28 % des fumeurs ont cessé de fumer.

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Soz.- Präventivmed. 50 (2005) 245–263

Table A1 Lung function, respiratory symptoms, body mass index and smoking in women of the SAPALDIA cohort, Switzerland

Lung function	**Female**							
Sapaldia 2 Age (years)	**n**	**FVC Percentiles (P)**						
		P10	**P25**	**P50**	**P75**	**P90**	**Mean**	**SD**
28–34	277	3.42	3.70	4.03	4.43	4.75	4.06	0.55
35–39	268	3.30	3.61	3.98	4.35	4.83	4.00	0.59
40–44	378	3.26	3.58	3.91	4.32	4.68	3.95	0.56
45–49	440	3.07	3.40	3.77	4.07	4.45	3.77	0.54
50–54	492	2.97	3.26	3.56	3.90	4.24	3.57	0.50
55–59	458	2.81	3.12	3.49	3.82	4.19	3.48	0.56
60–64	399	2.56	2.95	3.32	3.69	4.06	3.31	0.56
65–73	513	2.44	2.67	2.99	3.39	3.69	3.03	0.52
All	3225	2.76	3.16	3.59	4.00	4.39	3.59	0.64
		FEV1 Percentiles (P)						
28–34	278	2.75	3.02	3.30	3.59	3.82	3.29	0.45
35–39	267	2.64	2.86	3.17	3.45	3.81	3.18	0.46
40–44	381	2.52	2.80	3.07	3.38	3.60	3.07	0.45
45–49	447	2.33	2.57	2.85	3.15	3.43	2.86	0.45
50–54	493	2.17	2.43	2.68	2.97	3.20	2.69	0.41
55–59	462	2.05	2.30	2.60	2.87	3.09	2.58	0.43
60–64	401	1.88	2.17	2.42	2.71	2.96	2.42	0.44
65–73	505	1.68	1.89	2.17	2.43	2.70	2.17	0.41
All	3234	2.01	2.35	2.71	3.10	3.44	2.72	0.56

Symptoms	**Female (n=3978)**								
Sapaldia 2 Age (years)	**n**	**Wheeze**		**Chronic phlegm**		**Chronic cough**		**Shortness of breath**	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
28–34	352	0.07	0.26	0.05	0.21	0.03	0.18	0.18	0.38
35–39	320	0.07	0.25	0.05	0.22	0.06	0.23	0.18	0.39
40–44	449	0.08	0.28	0.07	0.25	0.06	0.24	0.22	0.41
45–49	541	0.08	0.27	0.05	0.23	0.04	0.21	0.27	0.44
50–54	596	0.09	0.28	0.06	0.24	0.06	0.24	0.31	0.46
55–59	567	0.08	0.27	0.09	0.28	0.07	0.25	0.39	0.49
60–64	495	0.06	0.24	0.08	0.28	0.05	0.22	0.38	0.49
65–73	658	0.08	0.27	0.06	0.24	0.07	0.25	0.46	0.50

Table A1 (continued)

BMI	Female									
Sapaldia 2 Age (years)		Percentiles (P)							change in bmi between Sapaldia 1 and 2	
	n	P10	P25	P50	P75	P90	Mean	SD	Mean	SD
28–34	284	19.22	20.50	22.09	24.91	28.83	23.34	4.33	1.85	2.57
35–39	277	19.24	20.37	22.16	25.21	28.68	23.26	4.23	2.00	2.25
40–44	391	19.43	20.79	23.03	25.96	29.00	23.99	4.88	2.17	2.70
45–49	455	19.81	21.21	23.63	26.75	30.38	24.54	4.65	2.16	2.24
50–54	514	20.32	21.80	24.48	28.01	31.79	25.41	4.92	2.31	2.45
55–59	485	20.24	21.98	24.82	28.50	32.67	25.74	4.88	2.15	2.14
60–64	426	21.38	23.07	25.67	29.10	32.99	26.35	4.54	1.91	2.33
65–73	560	21.50	23.60	26.39	30.11	33.52	27.11	4.90	1.79	2.25
All	3392	19.95	21.64	24.20	27.83	31.69	25.22	4.89	2.05	2.36

Smoking	Female										
Sapaldia 2 Age (years)				Cigarettes per day in current smokers							
		% current			Percentiles (P)						
	n	smokers	95 % CI	n	P10	P25	P50	P75	P90	mean	SD
28–34	351	25.4	20.9–30.2	89	1	4	10	15	20	10.3	7.7
35–39	319	32.6	27.5–38.0	103	3	7	15	20	20	13.5	9.3
40–44	446	28.5	24.3–32.9	127	2	6	15	20	25	14.6	9.7
45–49	537	31.1	27.2–35.2	167	3	6	15	20	30	14.9	10.3
50–54	591	26.9	23.4–30.7	159	3	10	15	20	30	16.0	10.2
55–59	561	24.1	20.6–27.8	135	2	6	15	20	20	13.7	8.8
60–64	491	17.5	14.2–21.2	85	2	4	10	20	25	12.6	9.6
65–73	652	9.5	7.3–12.0	62	2	5	14.5	20	30	14.9	11.1
All	3948	23.5	22.2–24.9	927	2	6	15	20	25	14.0	9.7

Table A2 Lung function, respiratory symptoms, body mass index and smoking in men of the SAPALDIA cohort, Switzerland

Lung function	**Male**							
Sapaldia 2 Age (years)	**n**	**FVC Percentiles (P)**						
		P10	**P25**	**P50**	**P75**	**P90**	**Mean**	**SD**
28–34	292	4.67	5.03	5.50	6.11	6.60	5.58	0.77
35–39	279	4.55	4.99	5.43	6.04	6.43	5.51	0.79
40–44	343	4.50	4.85	5.40	5.88	6.33	5.40	0.80
45–49	374	4.26	4.67	5.11	5.63	6.04	5.14	0.71
50–54	416	4.01	4.50	5.00	5.47	5.89	5.01	0.77
55–59	466	3.88	4.28	4.79	5.26	5.72	4.78	0.74
60–64	380	3.74	4.04	4.50	5.04	5.55	4.57	0.74
65–73	430	3.14	3.70	4.11	4.69	5.34	4.19	0.88
All	2980	3.85	4.38	4.98	5.54	6.08	4.96	0.90
		FEV1 Percentiles (P)						
28–34	298	3.61	3.92	4.34	4.72	5.21	4.36	0.62
35–39	281	3.54	3.86	4.28	4.67	5.01	4.26	0.64
40–44	341	3.37	3.75	4.15	4.50	4.86	4.13	0.62
45–49	378	3.13	3.50	3.86	4.26	4.61	3.86	0.60
50–54	415	2.92	3.29	3.73	4.11	4.48	3.71	0.65
55–59	466	2.73	3.11	3.52	3.92	4.22	3.47	0.63
60–64	382	2.58	2.95	3.30	3.67	4.09	3.30	0.62
65–73	427	2.08	2.47	2.92	3.34	3.76	2.90	0.67
All	2988	2.69	3.19	3.72	4.20	4.65	3.69	0.78

Symptoms	**Male (n=3695)**								
Sapaldia 2 Age (years)	**n**	**Wheeze**		**Chronic phlegm**		**Chronic cough**		**Shortness of breath**	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
28–34	377	0.13	0.33	0.07	0.26	0.04	0.19	0.09	0.28
35–39	353	0.11	0.31	0.09	0.29	0.07	0.25	0.10	0.29
40–44	414	0.09	0.29	0.09	0.29	0.04	0.20	0.11	0.31
45–49	452	0.08	0.26	0.09	0.28	0.04	0.21	0.14	0.34
50–54	503	0.09	0.28	0.09	0.29	0.06	0.24	0.17	0.38
55–59	576	0.07	0.26	0.08	0.28	0.05	0.21	0.20	0.40
60–64	472	0.08	0.28	0.14	0.34	0.07	0.25	0.26	0.44
65–73	548	0.10	0.31	0.14	0.35	0.06	0.23	0.30	0.46

Table A2 (continued)

BMI	Male									
Sapaldia 2 Age (years)		Percentiles (P)							change in bmi between Sapaldia 1 and 2	
	n	P10	P25	P50	P75	P90	Mean	SD	Mean	SD
28–34	311	21.31	22.82	24.61	26.70	29.09	25.08	3.42	2.79	2.32
35–39	294	21.50	23.16	25.33	27.47	29.48	25.58	3.69	2.17	2.08
40–44	362	21.89	23.74	25.45	27.77	30.68	25.97	3.75	2.07	1.98
45–49	396	21.80	23.66	25.58	28.10	31.28	26.15	3.76	1.77	1.96
50–54	441	22.63	24.09	26.22	28.74	31.80	26.86	4.05	1.80	2.03
55–59	516	23.25	24.97	26.91	29.41	32.70	27.44	3.70	1.82	1.88
60–64	415	22.79	24.73	26.73	29.05	31.90	27.10	3.53	1.31	1.92
65–73	470	23.17	25.01	27.35	29.72	32.31	27.56	3.75	1.29	2.01
All	3205	22.26	24.03	26.13	28.67	31.59	26.61	3.81	1.82	2.05

Smoking	Male										
Sapaldia 2 Age (years)				Cigarettes per day in current smokers							
		% current			Percentiles (P)						
	n	smokers	95 % CI	n	P10	P25	P50	P75	P90	mean	SD
28–34	372	29.6	25.0–34.4	110	1.5	7	15	20	30	16.6	13.1
35–39	346	34.0	29.1–39.2	118	1	6	20	20	30	16.1	11.6
40–44	350	34.6	30.0–39.4	143	1	7	20	30	35	18.6	13.9
45–49	413	36.0	31.6–40.7	160	<1	6.5	20	27.5	40	19.6	15.5
50–54	447	30.5	26.4–34.7	152	<1	3.5	20	22.5	30	16.2	13.0
55–59	499	27.4	23.7–31.2	157	<1	<1	12	20	30	14.1	13.7
60–64	574	26.3	22.3–30.6	123	<1	<1	12	20	30	13.6	12.8
65–73	467	20.3	17.0–24.0	110	<1	<1	8	20	20	10.4	10.2
All	3663	29.3	27.9–30.9	1073	<1	4	15	20	30	15.9	13.4