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COHORT PROFILE

Cohort Profile: Cohort of Norway (CONOR)

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How did the study come about?

A number of large population-based cardiovascular surveys have been conducted in Norway since the beginning of the 1970s. The surveys were carried out by the National Health Screening Service in cooperation with the universities and local health authorities. All surveys comprised a common set of questions, standardized anthropometric and blood pressure measurements and non-fasting blood samples that were analysed for serum lipids at the Ullevål Hospital Laboratory. These surveys provided considerable experience in conducting large-scale population-based surveys, thus an important background for the Cohort of Norway (CONOR). In the late 1980s the Research Council of Norway established a programme in epidemiology. This also gave stimulus to the idea of establishing a cohort including both core survey data and stored blood samples. In the early 1990s, all universities, the National Health Screening Service, The National Institute of Public Health and the Cancer Registry discussed the possibility of a national representative cohort.[1] The issue of storing blood samples for future analyses raised some concern and it was discussed in the parliament. In 1994, the Ministry of Health appointed the Steering Committee for the CONOR collaboration. In 1994–95, the fourth round of the Tromsø Study was conducted, and became the first survey to provide data and blood samples for CONOR. During the years 1994–2003, a number of health surveys that were carried out in other counties and cities also provided similar data for the network. So far, 10 different surveys have provided data and blood samples for CONOR (Figure 1). The administrative responsibility for CONOR was given to the Norwegian Institute of Public Health (NIPH) in 2002. The CONOR collaboration is currently a research collaboration between the NIPH and the Universities of Bergen, Oslo, Tromsø and Trondheim.

The purpose of CONOR

The CONOR cohort has not been established on the basis of any single hypothesis but is rather a multipurpose study. The ambition was to set up a sufficiently large enough cohort to study aetiological factors for a wide range of diseases. Additionally, this cohort should make it possible to describe Norwegian men and women in terms of distribution of exposures and health status according to time, place and socio-economic factors.

In 2002, CONOR and the Norwegian Mother and Child study (MoBa),[2] received a 5-year grant from the Norwegian Research Council to build a technology platform under the Functional Genomics programme (FUGE), called the Biobanks for Health in Norway (Biohealth) platform.[3] The overall aim was to investigate separate and combined effects of genes and environment on the risk of disease.

Who is in the sample?

Altogether 309 742 individuals were invited to the 10 surveys based on the 11-digit personal identifier and addresses from the Population Registry of Norway.[4] The goal is to include 200 000 participants. We defined those who attended the survey and/or answered at least one questionnaire and signed a written informed consent as participants. The numbers in Table 1 include individuals who participated and had given their written consent for research and linkage to health registries. A total of 7309 persons participated in two CONOR surveys, and one person participated in three. Thus, the total number of

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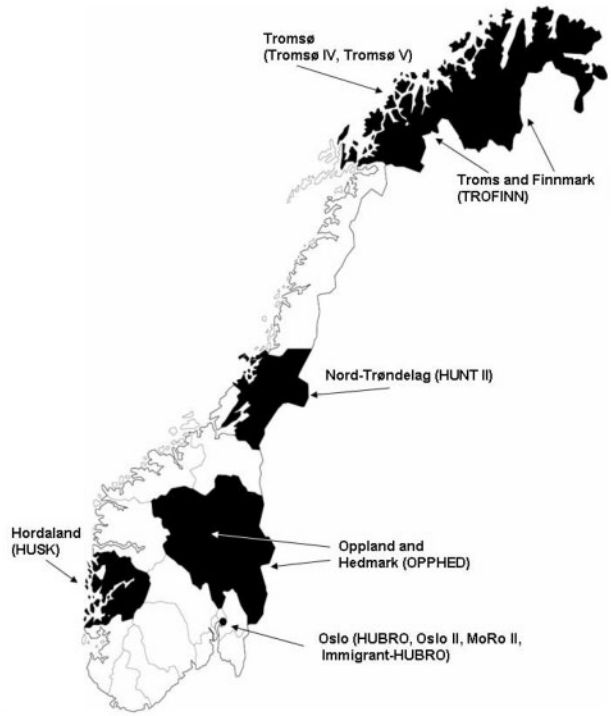

Figure 1 Map of Norwegian counties with location of each sub-study included in cohort of Norway (CONOR)

individuals in the CONOR cohort is 173 236. The distribution of age at the first examination and the number of deaths during follow-up through 2003 is given in Table 2. The individual surveys may have published papers with slightly different total numbers. Sampling procedures differed somewhat between the individual studies. The web site for each study contains more detailed information (Table 1).

What has been measured?

In all the CONOR surveys, the data collection followed a standard procedure. Letters of invitation were mailed about 2 weeks before the time of appointment and included a questionnaire and a brochure with the aims of the study and information about the examinations and procedures. At the screening, this initial questionnaire was collected from the attendees, participants underwent a physical examination and a non-fasting blood sample was drawn. In most studies, the participants were given one or two supplementary questionnaires, which they were instructed to fill in at home and return by mail in pre-addressed stamped envelopes.

About 4 weeks after attending the examination, a letter with selected results from the examination and blood tests was sent to all participants. Those with the highest scores of cardiovascular risk (a modified Framingham risk score based on multiplying the relative risks attributable to the subject's gender, serum cholesterol, systolic blood pressure the number of cigarettes currently smoked per day and family history of

Table 1 Number of invited and participating subjects in cohort of Norway (CONOR) 1994–2003

Name of the study	Year of survey	Number invited	Invited age-groups in years	Number of participants[a]			
				Men	Women	Total	Web address
Tromsø IV (The fourth Tromsø Study)	1994–1995	37 558	25+	12 797	14 128	26 925	http://uit.no/tromsoundersokelsen/tromso4/2
HUNT II (The second North-Trøndelag Study)	1995–1997	94 196	20+	30 441	34 576	65 017	http://www.hunt.ntnu.no/
HUSK (The Hordaland Health Study)	1997–1999	38 587	40–44, 46–47, 70–72	11 678	13 851	25 529	http://www.uib.no/isf/husk/
Oslo II (The second Oslo Study)	2000	14 209	48–77	6919		6919	http://www.fhi.no/artikler/?id=54685
HUBRO (The Oslo Health Study)	2000–2001	58 660	30, 31, 40, 45, 46, 59/60, 75/76	9509	11 852	21 361	http://www.fhi.no/artikler/?id=54464
OPPHED (The Oppland and Hedmark Health Study)	2000–2001	22 327	30, 40, 45, 60, 75	5602	6661	12 263	http://www.fhi.no/artikler/?id=28233
Tromsø V (The fifth Tromsø Study)	2001	10 353	30+	3440	4457	7897	http://uit.no/tromsoundersokelsen/tromso5/2
I-HUBRO (The Oslo Immigrant Health Study)	2002	12 088	20–60	1877	1737	3614	http://www.fhi.no/artikler/?id=28217
TROFINN (The Troms and Finnmark Health Study)	2002	16 229	30–77	4196	4836	9032	http://www.fhi.no/artikler/?id=28261
MoRo II (The second part of the Romsås in Motion Study)	2003	5535	34–70	896	1093	1989	http://www.fhi.no/artikler/?id=28254
CONOR (Cohort Norway)[a]	1994–2003	309 742	20–103				
Sum of participants				87 355	93 191	180 546	http://www.fhi.no/artikler/?id=28138
Sum of individuals				84 153	89 083	173 236	

[a]Number of participants equals those who attended the survey and agreed that information from the CONOR survey and blood samples can be linked to other registers and used in research. A total of 7310 individuals participated in more than one survey. Thus, the total number of individuals equals 173 236.

coronary heart disease) were advised to visit their own general practitioner, and in some cases offered a follow-up examination at the local hospital.[5]

Measures

Only a restricted core set of measurements and questionnaire responses constitute the CONOR data. Most individual studies that contribute to CONOR have more detailed measurements and questionnaire data. In the following section we describe the key core measurements that all studies contribute to CONOR; at the end we briefly describe some of the additional measurements that are in some of the contributing individual studies. All surveys were carried out in collaboration with the National Health Screening Service, Oslo (now the NIPH). Experienced and trained personnel conducted all procedures. Non-fasting serum total- and HDL-cholesterol, glucose and triglycerides were measured directly by an enzymatic method (Boehringer 148393, Boehringer-Mannheim, Federal Republic of Germany—from 2000 Hitachi 917 auto analyzer, Roche Diagnostic, Switzerland).

The Department of Clinical Chemistry, Ullevål University Hospital, Oslo, performed all laboratory assessments except for HUNT II (The second North-Trøndelag Study) where the analyses were performed at the Department of Clinical Chemistry, Levanger Hospital, Levanger. In Tromsø IV and V, cholesterol and triglycerides were measured at the Department of Clinical Chemistry, University Hospital North-Norway, Tromsø. Calibration procedures were carried out between these laboratories in connection with the surveys (Dr P.G. Lund-Larsen, National Health Screening Service, personal communication). An acceptable stability of the laboratory analyses over time in the population surveys has been reported.[6]

Heart rate, systolic and diastolic blood pressures were measured by an automatic device (DINAMAP, Criticon, Tampa, FL,USA). After 2 min of seated resting, three recordings were made at 1-min intervals. Mean values of the second and third systolic blood pressure measurements were used in calculating the cardiovascular risk score (CVD risk score) (Tverdal, 1989 5/id). The stability of the blood pressure measures has been evaluated and deemed acceptable.[7]

Body weight (in kilograms, one decimal) and height (in centimetres, one decimal) was measured according to a standard protocol with the participants wearing light clothing without shoes (manually recorded until 2000 and after that with an electronic Height and Weight Scale). Body mass index (BMI) was calculated as kilograms per square metre. Waist circumference was measured at the umbilicus to the nearest centimetre and with the subject standing and breathing normally. In obese individuals, waist circumference was defined as the midpoint between the iliac crest and lower margin of ribs. Hip circumference was measured as the maximum circumference around the buttocks. Both waist and hip were measured with a measuring tape of steel—which was emphasized to be placed horizontally. The waist–hip circumferences were used to calculate the waist–hip ratio.

Most individual studies that contribute to CONOR have several additional measurements—for example, extra samples of blood, ECG and ultrasonographic examination of carotid artery and abdominal aorta. Four of the study sites measured bone mineral density (DEXA and/or SXA) and have established a research group called Norwegian Epidemiologic Osteoporosis Studies (NOREPOS).[8] Altogether, around 28 000 individuals have had their bone mineral density measured and currently a number of collaborative studies are carried out.

The CONOR questions

All surveys used about 50 core CONOR questions agreed upon before the first CONOR survey in Tromsø in 1994. The exact wording of the questions is available at the CONOR website (http://www.fhi.no/dav/CA11310499.doc). Some questions have been slightly modified over the years.

The CONOR questions cover the following main topics: self-reported health and diseases such as diabetes, asthma, coronary heart disease, stroke and mental distress, musculo-skeletal pains, family history of disease, risk factors and lifestyle, social network and social support, education, work and housing, some types of occupation, use of medications and reproductive history (women).

Several of the questions have been evaluated or validated and deemed acceptable.[9–18] The Population Registry of Norway that was used to identify eligible subjects, contains information about gender, date of birth, marital status, address and country of birth.

Blood samples

Blood samples were drawn from the CONOR participants. EDTA blood for CONOR and the other sub-surveys have normally been collected in 7 or 5 ml vacutainers. These vacutainers were made by different manufacturers but were normally made of polypropylene. DNA has been extracted from more than 90 000 specimens to medio 2007, and Biohealth intends to extract DNA from all samples by Spring 2008. The extracted DNA and an additional sample of 1.25 ml EDTA-blood will be stored at a national biobank storage site at HUNT/NTNU biobank in Levanger (Mid-Norway).

What has been found?

Although a number of analyses from each participating study have been conducted, the CONOR file has only recently been compiled and made available for research. The first CONOR project was anchored in NOREPOS describing urban–rural differences in forearm fractures.[19] Other methodological and validation studies have been completed as described above.

What are the main strengths and weaknesses?

The CONOR database has several strengths: it is population based including populations from various parts of Norway, both rural and urban. The 11-digit personal identification number makes it possible to link cohort participants to national health registries. At present, several large linkages to other registers have been or are in the process of being conducted. These include linkages with census-based data for the whole population and the Medical Birth Registry of Norway, Disability Registry, Cancer Registry of Norway. Tables 2 and 3 present number of deaths and new cases of cancer in CONOR since date of examination by linkage to the death and cancer registries. Other large linkages include data from the Norwegian Drug Prescription Database and information from

Table 2 Number of participants (*n*) and number of deaths until December 31, 2003 in the cohort of Norway (CONOR) by age at inclusion in the surveys

	Men		Women	
Age (years)	*n*	Deaths	*n*	Deaths
<25	2037	15	2512	6
25–34	12 028	56	14 658	22
35–44	21 544	158	24 399	123
45–54	17 009	296	18 474	218
55–64	11 698	604	11 903	325
65–74	13 654	2008	9399	991
⩾75	6183	2138	7738	2141
Total	84 153	5279	89 083	3826

Table 3 Follow-up 1994–2006[a] of the CONOR cohort members. Number of cases of first cancer diagnosis in the Norwegian Cancer Registry after initial CONOR examination

	Men		Women	
	<70 years	⩾70 years	<70years	⩾70 years
Cancer site (ICD-7)				
Colorectal cancer (152-4)	582	631	528	476
Trachea, bronchus and lung (162)	191	300	133	110
Breast (170)	1	4	936	271
Prostate (177)	607	995	0	0
Bladder and other urinary organs (181)	102	235	33	51
Melanoma of skin (190)	170	89	238	82
All sites (including basal cell carcinoma of skin)	3180	3971	5411	2515

[a]Follow-up approximately through March 2006.

health surveys in several counties in the 1970s. There are also a number of disease registers that may be linked to the CONOR database. Earlier this year, the government passed a new legislation to make the national hospital discharge register personal identifiable, which would be possible to link to CONOR in the near future.

A major strength of CONOR is its sample size that means it would be able to make a unique contribution to establish main genetic effects and gene–environmental interactions, since precise and robust estimation of these effects requires very large sample sizes.[20,21] Our aim is to reach 200 000 individuals with blood samples and extracted DNA and we anticipate reaching this sample size by Spring 2008. For some hypotheses, it would be most efficient to employ a nested case control study design within CONOR, and we anticipate several such studies in the future. This comparatively large sample size means cases for a number of common and less common diseases may be identified from various sources.

There are some important weaknesses: the overall participation rate is 58% and is lowest in the surveys in Oslo and other urban areas and became lower throughout the study period. However, the overall participation rate is influenced by low participation rate in those aged ⩽30 years. The study population is somewhat heterogeneous as it includes sampling from 10 geographical areas with various age groups included over a 10-year period. The number of core variables is limited, and in some cases the wording of questions is slightly changed over the years.

Can I get hold of the data? Where can I find out more?

Guidelines have been developed for projects using data from CONOR (www.fhi.no). These shall ensure that projects will have a high scientific quality, facilitate quick publication of results from CONOR and make the data accessible for research. Research groups may apply for access. A project leader must be appointed. Researchers not residing in Norway are advised to seek contact with Norwegian counterparts. The study objectives should be within the broader aims of CONOR. Further details of these guidelines are provided at the CONOR website.

Applications and enquiries can be sent electronically to the Norwegian Public Health Institute (email: conor@fhi.no). Applications will be evaluated by the CONOR Steering Committee.

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