International Journal of Epidemiology, 2023, e80–e91
https://doi.org/10.1093/ije/dyac095
Advance Access Publication Date: 17 May 2022
Cohort Profile

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Cohort Profile Update: The HUNT Study, Norway

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Key Features

- In the HUNT Study, all residents aged ≥20 years in the Nord-Trøndelag region, Norway, have been invited to repeated surveys since 1984-86. The study data may be linked to local and national health registries.
- The HUNT4 survey in 2017-19 included 56 042 participants in Nord-Trøndelag and 107 711 participants in the neighbouring Sør-Trøndelag region.
- The HUNT4 data enable more long-term follow-up, studies of life course health trajectories and within-family studies.
- New measures include body composition analysis using bioelectrical impedance; a 1-week accelerometer recording; physical and cognitive testing in older adults; measurements of haemoglobin and blood cell counts, HbA1c and phosphatidylethanol; and genotyping.
- Researchers can apply for HUNT data access from HUNT Research Centre if they have obtained project approval from the Regional Committee for Medical and Health Research Ethics, see [www.ntnu.edu/hunt/data].

The original cohort

The Trøndelag Health Study (the HUNT Study) is a population-based cohort study of the adult population in Trøndelag County, Norway. It was previously called the Nord-Trøndelag Health Study, until the study in 2019 expanded to cover both regions of Trøndelag County, Nord-Trøndelag and Sør-Trøndelag. The study has been running in Nord-Trøndelag since 1984 and is designed to cover a broad range of health-related topics through repeated surveys with questionnaires, interviews, clinical examinations, laboratory measurements and storage of biological samples. Nord-Trøndelag is fairly representative of Norway except for the lack of large cities and immigrant populations, and the region is suitable for longitudinal studies due to low migration. The HUNT Study data can be linked to a wide range of local and national health registries by means of the unique identification number allocated to all Norwegian residents. All current residents ≥20 years of age in Nord-Trøndelag have been invited to each survey wave: the HUNT1 (1984–86, 77 202 participants, 89.4% of invitees participated),[1] HUNT2 (1995-97, 65 228 participants, 69.5%)[2] and HUNT3 (2006-08, 50 800 participants, 54.1%)[3] surveys (Figure 1). Since 1995-97, all adolescents (13-19 years of age) in Nord-Trøndelag have been invited to participate in the corresponding Young-HUNT Study.[4]

What is the reason for the new data collection?

In 2017–19, all adult residents of Trøndelag were invited to the HUNT4 survey. The reasons for this new survey were, first, to collect follow-up and extended information on previous participants, and new information on individuals having moved into the region or reached adult age. After completion of HUNT4, about 19 000 individuals have more than 30 years of follow-up spanning all four study cycles (Figure 1). The continued follow-up also allows for monitoring of secular trends in public health. Second, improved measurement methods have become available for several health and lifestyle characteristics important for public health, as described in the later sections. Third, the HUNT Study previously lacked data from a large city. In 2019, HUNT4 expanded to include a survey in Sør-Trøndelag, which includes the city of Trondheim with ∼202 000 inhabitants (2019). The extended study population from both Nord-Trøndelag and Sør-Trøndelag is generally representative of Norway (Supplementary Table S1, available as Supplementary data at *IJE* online). A fourth reason for new data collection is the expansion of genetic and molecular epidemiology, where 70 517 participants of the HUNT2 or HUNT3 surveys have been genotyped.

What will be the new areas of research?

Extended follow-up of HUNT participants and high attendance among older adults enable a stronger focus on disease incidence, progression and life course health trajectories. New generations of HUNT participants enable more within-family and intergenerational studies. More valid studies of physical activity and anthropometry are possible due to new data including accelerometer recordings and body composition analyses using bioelectrical impedance. Other new assessments include cognitive and physical testing in old age, fecal sampling for microbiome studies and metabolomics and proteomics analyses for deeper molecular phenotyping. With available genotype information, analyses are expanded to, for example, genome-wide association studies and Mendelian randomization.

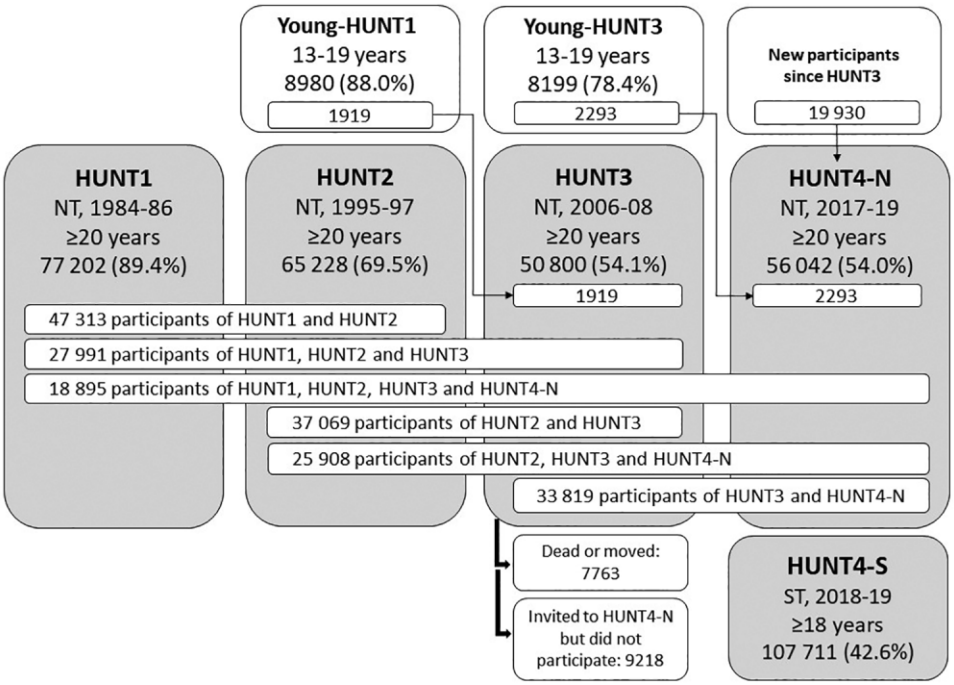

Figure 1 Flowchart of participation across the HUNT1–HUNT4 surveys and details on recruitment to HUNT4. The few individuals who have withdrawn their consent to participate in the HUNT Study have been excluded, and the numbers therefore deviate slightly from those reported in previous HUNT cohort profiles. NT, Nord-Trøndelag region; ST, Sør-Trøndelag region

Who is in the cohort?

In Nord-Trøndelag, all residents aged ≥20 years at the estimated time of survey participation were invited to HUNT4 between 29 August 2017 and 23 February 2019 (the HUNT4-N Survey). Out of 103 800 invitees, 56 042 (54.0%) participated, defined as returning the main questionnaire. Participation across the HUNT1-HUNT4 surveys is shown in Figure 1.

In Sør-Trøndelag, all residents aged ≥18 years were invited to the HUNT4-S Survey and 107 711 (42.6%) participated out of 252 991 invitees. HUNT4-S consisted of two parts: 1745 residents ≥70 years of age in districts of Trondheim municipality took part in an examination between 26 October 2018 and 12 June 2019, and the remainder took part in a questionnaire survey between 3 October 2019 and 19 November 2019.

With the completion of HUNT4-N, 123 004 residents in Nord-Trøndelag have participated in at least one HUNT survey, of whom 68 586 have participated in more than one survey and 5881 participated in the Young-HUNT Study as adolescents. With the completion of HUNT4-S, 230 617 individuals have participated in one or more of the HUNT surveys.

Characteristics of HUNT4 participants are given in Table 1. Participation in HUNT4 differed by age, being highest in the age groups 40-79 years, and also slightly differed by marital status and urban vs rural residency (Table 2). Attrition from HUNT3 to HUNT4 was highest in older adults and was also moderately higher among people with chronic diseases or poor self-rated health or who were smokers (Supplementary Table S2, available as Supplementary data at *IJE* online). Questionnaire surveys were performed among non-participants of HUNT4-N and previous HUNT participants who were not invited to HUNT4-N because they had emigrated from the study area (Table 3; Supplementary Table S3, available as Supplementary data at *IJE* online). Those who had emigrated reported lower body mass index (BMI), more physical activity, less smoking, better self-rated health and more frequent alcohol intake than both participants and non-participants. The non-participants had less healthy lifestyle, lower self-reported health and higher proportion of cardiovascular diseases, chronic obstructive pulmonary disease, diabetes and antihypertensive medication use.

What has been measured?

Similar to previous HUNT surveys, HUNT4-N consisted of questionnaires, a short interview, clinical examination and biological sampling, and was conducted by trained health professionals at examination stations in each of 23 municipalities in Nord-Trøndelag. HUNT4-S was mainly a web-based questionnaire survey (except for the examination of 1745 residents ≥70 years of age in Trondheim), but printed questionnaires were sent on

Table 1 Characteristics of participants in the HUNT4 Survey (HUNT4-N and HUNT4-S), reported as percentages[a] unless otherwise noted

Characteristics	HUNT4-N[b]		HUNT4-S[c]	
	Women ($n = 30\,574$)	Men ($n = 25\,468$)	Women ($n = 61\,066$)	Men ($n = 46\,645$)
Age (years), mean (SD, range)	53.9 (17.8, 19-102)[d]	54.8 (17.3, 19–101)[d]	49.9 (17.9, 18–105)	52.2 (17.7, 18–100)
Age groups (years)				
<30	11.9	11.0	16.8	13.7
30–39	12.7	11.3	15.7	13.6
40–49	16.6	15.4	17.2	16.7
50–59	19.0	19.4	19.2	19.4
60–69	18.8	21.3	16.1	18.6
70–79	14.2	15.6	10.2	13.2
80–89	5.6	5.2	3.9	4.4
≥90	1.2	0.7	0.8	0.5
Years of education[e]				
≤10	13.1	10.0	7.9	6.5
11–13	44.4	55.3	39.2	44.2
≥14	42.5	34.7	52.9	49.3
Married, registered partner or cohabitant	71.5	77.4	67.5	72.7
Living in urban constituency	39.6	37.3	56.3	56.3
Good or very good self-rated health	73.6	78.6	74.2	80.5
Daily smoking				
Never	56.1	55.9	71.2	68.9
Former	34.3	37.1	21.3	25.2
Current	9.6	7.0	7.5	5.9
Alcohol, units per week (median, IQR)[f]	1 (0–2.5)	2.5 (1–4.5)	1 (0–3)	3 (1–5.5)
Frequency of physical exercise				
≤ once/week	32.4	40.6	28.7	34.0
2–3 times/week	43.9	39.0	42.4	40.3
Almost every day	23.7	20.4	29.0	25.7
Self-reported history of current or previous disease				
Coronary heart disease (myocardial infarction or angina pectoris)	3.5	8.6	3.2	8.3
Atrial fibrillation	4.0	7.0	4.3	7.9
Stroke	2.9	4.1	2.1	3.3
Asthma	12.5	11.6	14.4	13.1
COPD	2.6	3.3	1.9	2.6
Diabetes	5.2	7.1	3.9	6.1
Hypo- or hyperthyroidism	12.1	3.3	12.1	3.7
Cancer	7.9	8.0	7.8	8.1
Sought health care for mental health problems	21.6	12.2	32.9	19.5
Current drug treatment				
Antihypertensive medication	21.4	25.6	15.6	21.8
Lipid-lowering medication	14.3	18.8	9.9	17.2
Medication for asthma or COPD	8.3	7.3	7.5	6.6
Medication for anxiety or depression	8.9	4.7	6.6	3.9
Medication for thyroid dysfunction	9.5	2.7	8.8	2.6
Visit to a general practitioner during the lpst 12 months	85.9	77.7	86.2	78.1
Admitted to hospital during the past 12 months	14.1	12.4	NA	NA
Body mass index[g] (kg/m^2), mean (SD)	26.9 (5.1)	27.6 (4.2)	25.8 (4.9)	26.7 (4.1)
Body mass index categories[g] (kg/m^2)				
<18.5	1.5	0.4	1.7	0.5
18.5–24.9	38.2	27.1	48.6	36.7
25.0–29.9	36.3	48.3	32.6	45.7
≥30.0	24.1	24.2	17.1	17.1

(Continued)

Table 1 Continued

Characteristics	HUNT4-N[b]		HUNT4-S[c]	
	Women ($n = 30\,574$)	Men ($n = 25\,468$)	Women ($n = 61\,066$)	Men ($n = 46\,645$)
Systolic blood pressure[h] (mmHg), mean (SD)	126.1 (19.4)	131.0 (16.9)	NA	NA
Diastolic blood pressure[h] (mmHg), mean (SD)	70.8 (9.4)	76.0 (10.3)	NA	NA
Low-density lipoprotein cholesterol[i] (mmol/l), mean (SD)	3.25 (0.97)	3.15 (0.96)	NA	NA
Estimated glomerular filtration rate[j] <60 ml/min/1.73m^2	6.6	6.2	NA	NA

COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation; NA, not available.

[a]Calculated among people with valid information, which ranges from 89% to 100% for individual items.

[b]The survey was conducted in Nord-Trøndelag between 29 August 2017 and 23 February 2019 (the survey includes a pilot study performed in May 2017). Characteristics are presented for the 56 042 individuals who participated in HUNT4-N by returning the main questionnaire. In addition, 897 individuals took part in the clinical examination, but did not return the questionnaire; these individuals were more often older adults included in the HUNT70+ study part that will be described in a separate paper.

[c]The survey was conducted in Sør-Trøndelag as a questionnaire survey between 3 October and 19 November 2019 (105 966 participants) or as an examination among residents ≥70 years in districts of Trondheim municipality between 26 October 2018 and 12 June 2019 (1745 participants). The 252 991 invitees to HUNT4-S include all adult residents of Sør-Trøndelag, except former Nord-Trøndelag residents who had moved to Sør-Trøndelag after previously participating in HUNT and were instead invited to an emigrant survey.

[d]All residents aged ≥20 years at the estimated time of survey participation were invited, and some were aged 19 years at the date of participation.

[e]Years of education based on self-reported level of education: primary school ≤10 years; academic or vocational school/apprentice 11–13 years; and university college or university ≥14 years.

[f]Units (12.8 g alcohol) calculated based on the self-reported usual number of glasses of beer/wine/liquor per 2 weeks or, if that information was missing, estimated from the reported frequency of alcohol consumption during the past year.

[g]For participants of the questionnaire survey in HUNT4-S, this was calculated from self-reported weight and height.

[h]Mean of the second and third measurements. For 0.4% of participants who had only two valid blood pressure measurements, we used the second measurement.

[i]Estimated using the equation developed by Sampson M *et al.*, *JAMA Cardiol* 2020;5:540–48.

[j]Estimated using the Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) equation.

request and to older adults. The HUNT4 questionnaires covered a broad range of topics including socioeconomic conditions, health-related behaviours, symptoms, conditions and diseases, as described in Table 3. Selected HUNT4-N participants were also asked to complete questionnaires related to specific health topics, and a 19% random sample aged 20-69 years was invited to complete a web-based food frequency questionnaire.[5] To evaluate the quality of the self-report of conditions in HUNT4, we compared the self-reported information with diagnostic codes recorded in the local or regional hospitals and on general practitioners' reimbursement forms. Compared with these diagnoses as a reference standard, the sensitivity, specificity and predictive values of the self-reported information varied across diagnoses in both HUNT4-N (Supplementary Table S4, available as Supplementary data at *IJE* online) and HUNT4-S (Supplementary Table S5, available as Supplementary data at *IJE* online). Of note, the diagnostic codes may be inaccurate and do not constitute a definite reference standard. For example, in absence of a more suitable diagnostic code, a disease diagnosis may likely be reported on the reimbursement form by a general practitioner if a patient comes for testing for that disease, even if the disease was not confirmed. In-depth validity studies have been conducted for self-reported headache[6] and insomnia[7] in HUNT4. Validity studies of self-report of, for example, diabetes,[8] psoriasis[9] and atrial fibrillation,[10] have been performed after previous HUNT surveys.

An overview of HUNT4 measurements, performed as part of the main HUNT4 examination or as ancillary data collections, is provided in Table 3. New aspects of the clinical examination in HUNT4-N compared with previous HUNT surveys included detailed body composition analysis using bioelectrical impedance (InBody 770, Cerritos, CA, USA), a 1-week accelerometer recording (AX3, Axivity, Newcastle, UK) and physical and cognitive testing [Short Physical Performance Battery (SPPB), grip strength and Montreal Cognitive Assessment, (MoCA); participants ≥70 years of age]. Blood pressure, pulse and peripheral capillary oxygen saturation were recorded three times at 1-min intervals using Dinamap CARESCAPE V100 (GE Healthcare, Chicago, IL, USA). Oral health clinical and radiographic examinations [Planmeca ProOne (orthopantomogram) and Planmeca Intra/Prostyle Intra with ProSensor HD (bitewing), Helsinki, Finland], hearing test (air-conduction pure-tone audiometry at 0.25-8 kHz according to ISO 8253-1 using Interacoustics audiometers type AD629 with TDH-39P supra-aural audiometric earphones) and spirometry (Jaeger Masterscope spirometers, JLAB version latest upgrade 2016, CareFusion, Würzburg, Germany) were performed in selected samples, and other tests have subsequently been performed in subgroups. All

Table 2 Relative probability of participation in HUNT4-N and HUNT4-S by sociodemographic characteristics

Characteristics	HUNT4-N				HUNT4-S			
	Women Participants, *n* (%)[a]	Relative probability[b] (95% CI)	Men Participants, *n* (%)[a]	Relative probability[b] (95% CI)	Women Participants, *n* (%)[a]	Relative probability[b] (95% CI)	Men Participants, *n* (%)[a]	Relative probability[b] (95% CI)
Total invited population	30 574 (58.8%)		25 468 (49.1%)		61 066 (48.9%)		46 645 (36.4%)	
Age (years)								
<30	3643 (43.5)	1.00 (reference)	2811 (31.0)	1.00 (reference)	10 289 (38.4)	1.00 (reference)	6396 (21.6)	1.00 (reference)
30–39	3870 (52.5)	1.21 (1.17, 1.25)	2881 (38.1)	1.23 (1.18, 1.28)	9591 (46.3)	1.20 (1.18, 1.23)	6327 (27.9)	1.29 (1.26, 1.33)
40–49	5087 (59.1)	1.36 (1.32, 1.40)	3908 (45.2)	1.46 (1.40, 1.52)	10 532 (52.9)	1.38 (1.35, 1.40)	7784 (36.8)	1.70 (1.66, 1.75)
50–59	5817 (65.7)	1.51 (1.47, 1.56)	4948 (53.9)	1.74 (1.68, 1.80)	11 728 (59.5)	1.55 (1.52, 1.58)	9044 (44.4)	2.06 (2.00, 2.11)
60–69	5745 (69.9)	1.61 (1.56, 1.65)	5430 (63.8)	2.06 (1.99, 2.13)	9851 (59.3)	1.54 (1.51, 1.57)	8677 (52.1)	2.41 (2.35, 2.48)
70–79	4329 (67.8)	1.56 (1.51, 1.61)	3978 (65.3)	2.11 (2.03, 2.18)	6253 (47.5)	1.24 (1.21, 1.26)	6151 (49.5)	2.29 (2.23, 2.36)
80–89	1725 (54.1)	1.25 (1.20, 1.30)	1327 (56.5)	1.82 (1.74, 1.91)	2357 (38.3)	1.00 (0.96, 1.03)	2041 (46.0)	2.13 (2.05, 2.21)
≥90	358 (37.5)	0.86 (0.79, 0.94)	185 (41.9)	1.35 (1.20, 1.51)	465 (25.2)	0.66 (0.61, 0.71)	225 (29.7)	1.38 (1.23, 1.54)
Marital status								
Married or registered partner	15 184 (66.5)	1.00 (reference)	14 092 (60.3)	1.00 (reference)	27 230 (55.7)	1.00 (reference)	24 033 (47.2)	1.00 (reference)
Not married or registered partner	8775 (50.2)	0.89 (0.87, 0.90)	8130 (37.2)	0.78 (0.76, 0.80)	22 687 (44.6)	0.92 (0.91, 0.93)	16 848 (26.9)	0.76 (0.74, 0.77)
Divorced, separated or widow(er)	6549 (56.6)	0.86 (0.85, 0.88)	3188 (48.5)	0.79 (0.76, 0.81)	11 085 (44.2)	0.83 (0.82, 0.85)	5743 (39.8)	0.81 (0.79, 0.82)
Constituency type								
Urban	12 063 (55.5)	1.00 (reference)	9470 (46.4)	1.00 (reference)	33 399 (46.2)	1.00 (reference)	25 537 (34.3)	1.00 (reference)
Rural	18 411 (61.1)	1.09 (1.07, 1.11)	15 921 (50.8)	1.07 (1.05, 1.09)	26 660 (53.6)	1.14 (1.13, 1.15)	20 371 (39.7)	1.04 (1.03, 1.06)

[a]Percentage among the total number of invitees in the category.
[b]Age-adjusted relative probability of participation.

Table 3 Content of the HUNT4-N and HUNT4-S surveys

Study parts and data collection method	Selection criteria	Participants, *n* (% of those invited)	Content
HUNT4-N (Nord-Trøndelag region)			
		Questionnaires (Q)	
Q1 Web/printed	All residents of Nord-Trøndelag aged ≥20 years. Answered prior to attending the examination	56 042 (54.0)	Quality of life, diseases and illnesses, medication, health care use, lifestyle, screen-based activity, growing up, socioeconomics
Q2 Web/printed	All responders to Q1, answered at the screening station or returned in prepaid envelopes	42 763 (77.0)	Social network, diet, broad range of symptoms, cultural activities, life events, sexuality, work, pregnancies and birth control, activities of daily living. Different questionnaires by sex and age
Q3 Arthritis Printed	Participants reporting: (i) rheumatoid arthritis or spondylarthritis; (ii) joint pain and psoriasis; and (iii) random 5% reporting joint pain but not psoriasis	3775 (80.9)	Diagnosis, family history, use of medication, symptom load, physical function
Q3 Diabetes Printed	Participants reporting diabetes	2393 (73.5)	Age of onset, symptoms, use of medications, complications, challenges
Q3 Diet Printed	19.3% random sample among participants 20–69 years[a]	5025 (58.9)	FFQ assessing the habitual total dietary intake in adults, including 281 questions about food items, meals and dietary supplements
Q3 CAM Printed	Participants reporting use of CAM in past 12 months	4145 (78.7)	Type, frequency, effect of and reasons for use of CAM
Q3 Oral health Printed	20% random sample of HUNT4 participants and participants in the HUNT3 Dental Health Study	7435 (66.8)	Use of dental services, oral hygiene habits, oral health-related quality of life (OHIP-14)
Q Non-participation Printed	Anonymous questionnaire 20% random sample of non-participants in HUNT4-N	1320 (13.9)	Quality of life, lifestyle, diseases and reasons for nonparticipation
Emigration study Web	All previous participants in HUNT1-3 or Young-HUNT1-3 having moved out of Nord-Trøndelag before invitation to HUNT4-N	5219 (35.8)	Similar to Q1 and Q2
		At the examination stations	
Interview	All participants	53 806 (96.0)	Ethnicity, sources of subsistence, work, reproductive factors
Clinical measurements	All participants	53 816 (96.0) 51 477 (91.9)[b]	Blood pressure, pulse, peripheral oxygen saturation, height, weight, body composition (bioelectrical impedance analysis)
Physical activity and sleep	All participants (if available sensors)	31 295 (55.8)	Diary of time at work Accelerometer sensors on the thigh and lower back for one week
Oral health	20% random sample of HUNT4 participants and participants in the HUNT3 Dental Health Study[c,d]	4933 (67.0)	Clinical examination (dental caries, periodontal status and oral mucosa), radiographic examination (OPG and BW), saliva for microbiome analysis
Hearing	All participants in larger municipalities[d]	28 411 (83.5)	Hearing test, questionnaire on hearing loss, exposure to noise, tinnitus
Lung study	10% random sample and those reporting symptoms, medication or diagnosis of obstructive lung disease Age 19–85 years	15 727 (82.4)	Interview on symptoms, exacerbations, diagnosis, use of medication and health status. Prebronchodilator spirometry
HUNT70+	Everyone aged ≥70 years	9930	Tests of cognitive and physical functions, to be described in detail in a separate publication

(Continued)

Table 3 Continued

Study parts and data collection method	Selection criteria	Participants, *n* (% of those invited)	Content
Blood samples	All participants	54 500	Tests performed included any of the following: haemoglobin, blood cell counts, creatinine, total and HDL cholesterol, triglycerides, HbA1c, CRP, troponin I, TSH (free thyroxine and TPO antibodies in subgroups), coeliac serology, PEth
	Buffy coat for DNA extraction	52 772	DNA extraction and genotyping
	Plasma	52 830	Stored at -80 °C and -196 °C for future analyses
	Serum	54 500	Stored at -80 °C and -196 °C for future analyses
Urine samples	Previous participants of HUNT2 and 3 Microalbuminuria Study and ∼40% random samples in large and some small municipalities, limited by logistic factors	26 961	Analysed: creatinine, albumin Stored at -80 °C for future analyses
Saliva samples	30 % random sample in the same municipalities as for urine samples	17 111	Stored at -80 °C for future analyses
Feces samples	All participants, invited after or at the time of participation (if available sample kit)	13 300 (24.9)	Ongoing microbiome analyses
	Ancillary studies, performed after the main clinical examination		
Fitness	Self-reported or hospital-diagnosed atrial fibrillation at HUNT3 or 4, and participants in the HUNT3 or Young-HUNT3 Fitness Study or HUNT3 Echo Study	2448 (42.5)	Cardiopulmonary exercise test (CPET) Interview
Heart	Same as for Fitness	2448 (42.5)	Echocardiography Pulse wave velocity by Doppler ($n = 852$)
Cognitive function	All participants	5236 (9.3)	Web-based cognitive tests
Osteoporosis	Participants in HUNT2, 3 or 4 Osteoporosis or Lung Study	8450 (72.0)	Dual-energy X-ray absorptiometry (DXA) of hip and lumbar spines
Psychiatry	Random sample aged 20–65 years	2092 (21.8)	1–2-h structured interview on mental symptoms, treatment and use of drugs
MRI brain	Participants in HUNT3 MRI-study and 15% random sample of HUNT4 participants aged 20–66 years resident in Levanger or Verdal municipalities	1100 by 31 December 2021	MRI of brain, planned to include 1200 persons. Data collection continues until July 2022
Coeliac disease	All participants with positive coeliac serology ($n = 1100$)	500 (67) by 31 December 2021	Questionnaire, endoscopy with biopsies, sampling of blood, feces and saliva, ongoing data collection. Ongoing, planned to include 800 people. Data collection phase I continues until July 2022
HUNT4-S (Sør-Trøndelag region)			
Q1 Web or printed	All residents of Sør-Trøndelag aged ≥18 years, unless they participated in the HUNT4-S70+ study or were included in the HUNT4-N emigration study	105 966 (42.8)	Similar to Q1 in HUNT4-N
HUNT4-S70+	Residents ≥70 years in districts of Trondheim municipality	1745 (33.8)	Similar to HUNT70+

BW, bitewing; CAM, complementary and alternative medicine; CRP, C-reactive protein; FFQ, Food Frequency Questionnaire; HDL, high-density lipoprotein; MRI, magnetic resonance imaging; OPG, orthopantomogram; PEth, phosphatidylethanol; Q, questionnaire; TPO, thyroid peroxidase, TSH, thyroid stimulating hormone.

[a]No overlap with random samples for the lung study, the osteoporosis study or the arthritis study. Overlap with the Oral Health Study.

[b]The number 51 477 refers to the body composition analysis, which had fewer participants as not all participants could be measured barefoot.

[c]No overlap with random sample for the lung study, the osteoporosis study or the arthritis study.

[d]Examinations only in larger municipalities (Stjørdal, Levanger, Verdal, Steinkjer, Namsos and Nærøy), but questionnaires in all municipalities.

participants provided blood samples drawn in a non-fasting state between 9 am and 8 pm and time since last meal was recorded. Biological sampling at the field stations included blood, urine and saliva, and feces kits were returned in pre-paid envelopes. Biological material was handled at the field stations according to appropriate standards and transported to the biobank every evening in a cold chain. For all participants, two blood tubes were delivered at the laboratory of Levanger Hospital, Nord-Trøndelag Hospital Trust the next day for immediate analyses or transport to other laboratories. New analyses in blood included haemoglobin (Hb) and blood cell counts, HbA1c and phosphatidylethanol (PEth, an indicator of alcohol intake). Three blood tubes were aliquoted and stored in automated freezers in HUNT Biobank.

Since the publication of the original cohort profile in 2013,[3] new analyses of biological material stored in HUNT Biobank include the genotyping of 70 517 participants of HUNT2 or HUNT3, genotyping of 18 098 additional participants of HUNT4-N,[11] and SomaLogic's SomaScan proteomics analyses[12] and measurements of vitamin D[13] and troponin I[14] in subsamples.

The HUNT participants have consented to linkage to the many high-quality health and administrative registries in Norway, and to information from medical records. Such linkages can be reliably made using the national identification numbers allocated to all Norwegian residents, and means that prospectively recorded information on health outcomes can be obtained also for participants who do not attend subsequent HUNT surveys. An overview of Norwegian health registries is given by the Directorate for e-Health at Helsedata.no [https://helsedata.no/en/].

What has it found? Key findings and publications

In Table 1, we present descriptive characteristics of the HUNT4-N and HUNT4-S participants, including prevalence estimates of a range of chronic conditions and diseases. The longitudinal nature of HUNT enables analyses of long-term population changes in health-related factors. For example, comparison of HUNT4-N with previous HUNT surveys shows how the prevalence of smoking, high blood pressure and atherogenic lipid levels has declined from the 1980s until now, whereas the prevalence of obesity and diabetes has increased (Figure 2; Supplementary Table S6, available as Supplementary data at *IJE* online). Although the prevalence of diabetes has increased, HbA1c measurements in HUNT4 indicate that the current prevalence of undiagnosed diabetes is low.[15] The prevalence of tension-type headache has increased, whereas migraine and medication overuse headache have become less common,[16] as has hearing impairment.[17] Information from HUNT4 has further enabled prevalence estimates of dementia, mild cognitive impairment,[18] periodontitis[19] and depression and anxiety symptoms,[20] and estimation of the longitudinal decline in VO_{2peak}.[21] Analyses of HUNT4 have further shown that shift work is associated with higher levels of C-reactive protein and chronic musculoskeletal pain,[22] and that cognitive impairment is associated with lower physical performance.[23]

The new focus on genetic and molecular epidemiology has resulted in, for example, genome-wide association studies (GWAS) identifying new genetic variants associated with atrial fibrillation,[24] serum lipids,[25] thyroid stimulating hormone (TSH)[26] and bone mineral density.[27] Mendelian randomization studies have examined the causal associations between serum lipids and kidney function[28] and provided support for the causal role of smoking heaviness on mortality,[29] of higher body mass on psoriasis[30] and bloodstream infections[31] and of PCSK9 on serum cholesterol and coronary heart disease.[32] Anthropometric measures spanning 6 decades have demonstrated how body mass index (BMI) increases more strongly in genetically predisposed individuals during transition to a more obesogenic environment.[33,34] The predictive value of circulating proteins in secondary cardiovascular events has been examined using proteomics analyses.[12] The large number of relatives participating in HUNT has enabled within-family studies. Parent-offspring analyses have suggested that maternal intrauterine environment, as proxied by maternal single nucleotide polymorphisms (SNPs) that influence offspring birthweight, is unlikely to be a major determinant of adverse cardiometabolic outcomes in population-based samples of offspring.[35] Within-family Mendelian randomization analyses have enabled correction for familial biases in, for example, studies of the effects of height and body mass on educational attainment.[36] Supplementary Table S7 (available as Supplementary data at *IJE* online) provides examples of studies showing how HUNT data have been used across a range of health topics since the original cohort profile was published in 2013.

What are the main strengths and weaknesses?

HUNT is suitable for longitudinal studies due to the long-term follow-up with repeated measurements since the 1980s, low migration, possibilities for registry linkages, and available valid information on migration and deaths from the National Population Register. The HUNT surveys cover a broad range of health-related topics, and many questionnaire items have been kept unchanged across the surveys to enable longitudinal comparisons. Quality-

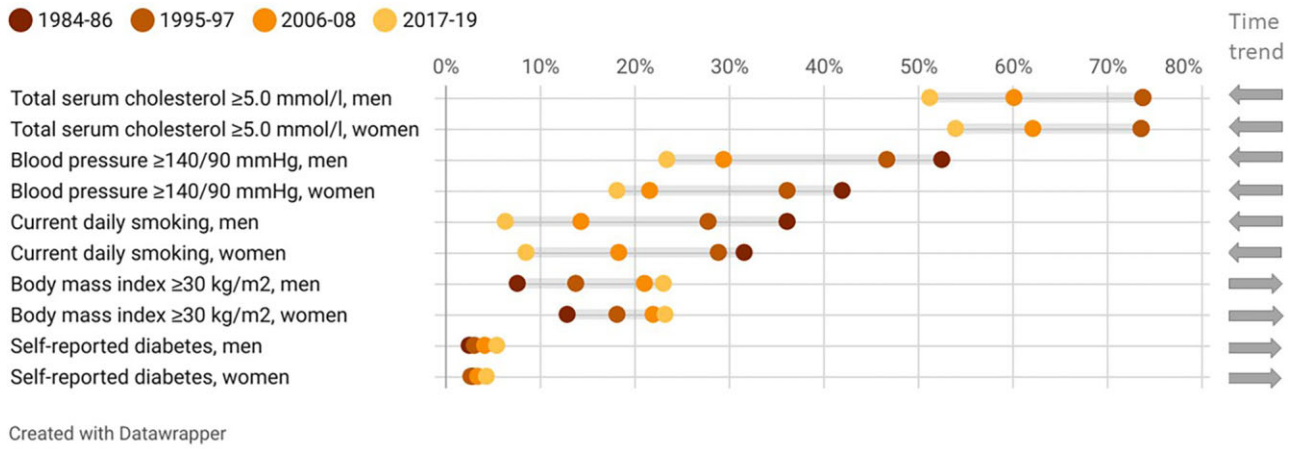

Figure 2 Prevalence of cardiovascular risk factors in HUNT1 (1984–86), HUNT2 (1995–97), HUNT3 (2006–08) and HUNT4-N (2017–19), by sex, age-standardized (direct method using 10-year age categories) to the Norwegian population 20 years and older on 1 January 2020. Point estimates with 95% confidence intervals are provided in Supplementary Table S6 (available as Supplementary data at *IJE* online)

controlled HUNT data are stored at the HUNT Databank and biological material is stored in the state-of-the-art HUNT Biobank at the HUNT Research Centre, Levanger.

As the HUNT Study has invited the entire population in the area over decades, the study population includes many family members, both siblings and across generations, and is therefore suitable for within-family studies. A particular asset compared with many other studies is available offspring information in adult age.[37–39] The study population has cryptic relatedness that may have to be considered in the analytical approach of, for example, GWAS, but is quite outbred with a mean inbreeding coefficient[40] of 0.0024 (calculated using KING software[41]).

The relatively high participation indicates a generally lower concern for selection bias. Nevertheless, attrition from HUNT3 to HUNT4 was somewhat higher among participants with chronic diseases or other indices of ill health, and lifestyle differed among non-participants and migrants compared with participants of HUNT4. To inform about selective participation by ill health among all HUNT4 invitees, we also examined primary health care diagnostic codes across a range of diseases, as well as primary health care use, for HUNT4 invitees and participants recorded during the calendar year 2017 (for HUNT4-N) or 2019 (for HUNT4-S). The proportion being assigned each diagnostic code generally did not differ substantially between participants and invitees, but results vary between diagnoses as detailed in Supplementary Table S8 (available as Supplementary data at *IJE* online). For example, a dementia diagnosis was less often recorded among participants than among invitees. General practice visits were more frequent among participants than non-participants at ages >80 years. In contrast, home nursing and nursing home residency were more common among non-participants (Supplementary Figure S1, available as Supplementary data at *IJE* online). The ethnically homogeneous population limits the generalizability to people of non-European ancestry.

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

Researchers affiliated to a Norwegian research institution can apply for HUNT data access from HUNT Research Centre [www.ntnu.edu/hunt] if they have obtained project approval from the Regional Committee for Medical and Health Research Ethics (REC). Researchers not affiliated to a Norwegian research institution should collaborate with and apply through a Norwegian principal investigator. Information on the application and conditions for data access is available at [www.ntnu.edu/hunt/data]. The HUNT Databank website provides a detailed overview of the available variables in HUNT [www.ntnu.edu/hunt/databank]. Certain data from ancillary HUNT projects may be subject to a time-limited exclusivity provided to the researchers who have financed and conducted the data collection. Biological material is available for analyses, and information on procedures is found at the HUNT Biobank website [https://www.ntnu.edu/hunt/hunt-biobank]. Data from the health registries are not kept by HUNT; instead, linkages between HUNT and registry data have to be made for each research project and require that the principal investigator has obtained project-specific approval for such linkage by REC and each registry owner.

Ethics approval

The work presented in this Cohort Profile Update was approved by the Mid-Norway Regional Committee for Medical and Health Research Ethics (REK midt 67445).

Data availability

See 'Can I get hold of the data?' above.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

B.O.Å., A.L., T.A.R., G.K., T.V.G., E.P.S., J.S.F., J.H., O.H., M.C.S., S.A.A.V., H.K.S., P.T., E.R.S., G.S., P.J.M., V.R., K.H., M.N. and S.K. participated in planning, conduct or data handling of the HUNT4 Survey. B.O.Å. and A.L. planned the Cohort Profile Update and analysed the data with contributions from T.V.G., J.S.F., J.H., B.M.B. and E.R.S. B.O.Å. and A.L. drafted the manuscript, and all authors revised the manuscript. Guarantor: B.O.Å.

Funding

The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Trøndelag County Council, Central Norway Regional Health Authority and the Norwegian Institute of Public Health.

Acknowledgements

We thank the population of Trøndelag for their willingness to contribute with important data and biological material, and politicians and administrations in all municipalities for positive attitude and support of logistics. We thank the administrative staff at HUNT Research Centre for comprehensive contribution to the planning, performance, collection and storage of data and biological material. For this Cohort Profile Update, Nord-Trøndelag Hospital Trust provided diagnostic codes from Nord-Trøndelag Hospital Trust and St. Olavs Hospital, and the Norwegian Directorate of Health provided data from the KUHR database and the Norwegian Registry for Primary Health Care. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Registry for Primary Health Care is intended nor should be inferred.

Conflict of interest

None declared.

References

1. Holmen J, Midthjell K, Bjartveit K *et al.* The Nord-Trøndelag Health Survey 1984–1986. Purpose, background and methods. Participation, Non-Participation and Frequency Distributions. Report No 4. Verdal, Norway: Statens Institutt for folkehelse, Senter for samfunnsmedisinsk forskning, 1990.
2. Holmen J, Midthjell K, Krüger Ø *et al.* The Nord-Trøndelag Health Study 1995-97 (HUNT 2): objectives, contents, methods and participation. *Norsk Epidemiologi* 2003;**13**:19–32.
3. Krokstad S, Langhammer A, Hveem K *et al.* Cohort Profile: The HUNT Study, Norway. *Int J Epidemiol* 2013;**42**:968–77.
4. Holmen TL, Bratberg G, Krokstad S *et al.* Cohort profile of the Young-HUNT Study, Norway: a population-based study of adolescents. *Int J Epidemiol* 2014;**43**:536–44.
5. Carlsen MH, Lillegaard IT, Karlsen A, Blomhoff R, Drevon CA, Andersen LF. Evaluation of energy and dietary intake estimates from a food frequency questionnaire using independent energy expenditure measurement and weighed food records. *Nutr J* 2010;**9**:37.
6. Hagen K, Asberg AN, Uhlig BL, Tronvik E, Brenner E, Sand T. The HUNT4 study: the validity of questionnaire-based diagnoses. *J Headache Pain* 2019;**20**:70.
7. Filosa J, Omland PM, Langsrud K *et al.* Validation of insomnia questionnaires in the general population: the Nord-Trondelag Health Study (HUNT). *J Sleep Res* 2021;**30**:e13222.
8. Midthjell K, Holmen J, Bjorndal A, Lund-Larsen G. Is questionnaire information valid in the study of a chronic disease such as diabetes? The Nord-Trondelag diabetes study. *J Epidemiol Community Health* 1992;**46**:537–42.
9. Modalsli EH, Snekvik I, Asvold BO, Romundstad PR, Naldi L, Saunes M. Validity of self-reported psoriasis in a general population: the HUNT study, Norway. *J Invest Dermatol* 2016;**136**:323–25.
10. Malmo V, Langhammer A, Bonaa KH, Loennechen JP, Ellekjaer H. Validation of self-reported and hospital-diagnosed atrial fibrillation: the HUNT study. *Clin Epidemiol* 2016;**8**:185–93.
11. Brumpton BM, Graham S, Surakka I *et al.* The HUNT Study: a population-based cohort for genetic research. *medRxiv*, https://doi.org/10.1101/2021.12.23.21268305, 25 December 2021, preprint: not peer reviewed.
12. Ganz P, Heidecker B, Hveem K *et al.* Development and validation of a protein-based risk score for cardiovascular outcomes among patients with stable coronary heart disease. *JAMA* 2016;**315**:2532–41.
13. Larose TL, Chen Y, Camargo CA Jr, Langhammer A, Romundstad P, Mai XM. Factors associated with vitamin D deficiency in a Norwegian population: the HUNT Study. *J Epidemiol Community Health* 2014;**68**:165–70.
14. Lyngbakken MN, Rosjo H, Holmen OL, Dalen H, Hveem K, Omland T. Temporal changes in cardiac troponin I are associated with risk of cardiovascular events in the general population: the Nord-Trondelag Health Study. *Clin Chem* 2019;**65**:871–81.
15. Stene LC, Ruiz PL, Asvold BO *et al.* How many people have diabetes in Norway in 2020? *Tidsskr nor Laegeforen* 2020;**140**:1750–53.
16. Hagen K, Stovner LJ, Zwart JA. Time trends of major headache diagnoses and predictive factors. Data from three Nord-Trondelag health surveys. *J Headache Pain* 2020;**21**:24.
17. Engdahl B, Strand BH, Aarhus L. Better hearing in Norway: a comparison of two HUNT cohorts 20 years apart. *Ear Hear* 2021;**42**:42–52.
18. Gjora L, Strand BH, Bergh S *et al.* Current and future prevalence estimates of mild cognitive impairment, dementia, and its subtypes in a population-based sample of people 70 years and older in Norway: the HUNT study. *J Alzheimers Dis* 2021;**79**:1213–26.
19. Stodle IH, Verket A, Hovik H, Sen A, Koldsland OC. Prevalence of periodontitis based on the 2017 classification in a Norwegian population: The HUNT study. *J Clin Periodontol* 2021;**48**:1189–99.

20. Bojanic I, Sund ER, Sletvold H, Bjerkeset O. Prevalence trends of depression and anxiety symptoms in adults with cardiovascular diseases and diabetes 1995-2019: the HUNT studies, Norway. *BMC Psychol* 2021;**9**:130.
21. Letnes JM, Dalen H, Aspenes ST, Salvesen Ø, Wisløff U, Nes BM. Age-related change in peak oxygen uptake and change of cardiovascular risk factors. The HUNT Study. *Prog Cardiovasc Dis* 2020;**63**:730–37.
22. Matre D, Christensen JO, Mork PJ, Ferreira P, Sand T, Nilsen KB. Shift work, inflammation and musculoskeletal pain: The HUNT Study. *Occup Med* 2021;**71**:422–27.
23. Sverdrup K, Selbæk G, Bergh S *et al.* Physical performance across the cognitive spectrum and between dementia subtypes in a population-based sample of older adults: the HUNT study. *Arch Gerontol Geriatr* 2021;**95**:104400.
24. Nielsen JB, Thorolfsdottir RB, Fritsche LG *et al.* Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nat Genet* 2018;**50**:1234–39.
25. Nielsen JB, Rom O, Surakka I *et al.* Loss-of-function genomic variants highlight potential therapeutic targets for cardiovascular disease. *Nat Commun* 2020;**11**:6417.
26. Zhou W, Brumpton B, Kabil O *et al.* GWAS of thyroid stimulating hormone highlights pleiotropic effects and inverse association with thyroid cancer. *Nat Commun* 2020;**11**:3981.
27. Surakka I, Fritsche LG, Zhou W *et al.*; Regeneron Genetics Center. MEPE loss-of-function variant associates with decreased bone mineral density and increased fracture risk. *Nat Commun* 2020;**11**:4093.
28. Rasheed H, Zheng J, Rees J *et al.* The causal effects of serum lipids and apolipoproteins on kidney function: multivariable and bidirectional Mendelian-randomization analyses. *Int J Epidemiol* 2021;**50**:1569–79.
29. Vie GA, Wootton RE, Bjorngaard JH *et al.* The effect of smoking intensity on all-cause and cause-specific mortality-a Mendelian randomization analysis. *Int J Epidemiol* 2019;**48**:1438–46.
30. Budu-Aggrey A, Brumpton B, Tyrrell J *et al.* Evidence of a causal relationship between body mass index and psoriasis: a mendelian randomization study. *PLoS Med* 2019;**16**:e1002739.
31. Rogne T, Solligard E, Burgess S *et al.* Body mass index and risk of dying from a bloodstream infection: a Mendelian randomization study. *PLoS Med* 2020;**17**:e1003413.
32. Brumpton BM, Fritsche LG, Zheng J *et al.* Variation in serum PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9), cardiovascular disease risk, and an investigation of potential unanticipated effects of PCSK9 inhibition. *Circ Genom Precis Med* 2019;**12**:e002335.
33. Brandkvist M, Bjørngaard JH, Ødegård RA, Åsvold BO, Sund ER, Vie GÅ. Quantifying the impact of genes on body mass index during the obesity epidemic: longitudinal findings from the HUNT Study. *BMJ* 2019;**366**:l4067.
34. Brandkvist M, Bjørngaard JH, Ødegård RA *et al.* Genetic associations with temporal shifts in obesity and severe obesity during the obesity epidemic in Norway: a longitudinal population-based cohort (the HUNT Study). *PLoS Med* 2020;**17**:e1003452.
35. Moen GH, Brumpton B, Willer C *et al.* Mendelian randomization study of maternal influences on birthweight and future cardiometabolic risk in the HUNT cohort. *Nat Commun* 2020;**11**:5404.
36. Brumpton B, Sanderson E, Heilbron K *et al.*; 23andMe Research Team. Avoiding dynastic, assortative mating, and population stratification biases in Mendelian randomization through within-family analyses. *Nat Commun* 2020;**11**:3519.
37. Alsnes IV, Vatten LJ, Fraser A *et al.* Hypertension in pregnancy and offspring cardiovascular risk in young adulthood: prospective and sibling studies in the HUNT study (Nord-Trondelag Health Study) in Norway. *Hypertension* 2017;**69**:591–98.
38. Carslake D, Davey Smith G, Gunnell D, Davies N, Nilsen TIL, Romundstad P. Confounding by ill health in the observed association between BMI and mortality: evidence from the HUNT Study using offspring BMI as an instrument. *Int J Epidemiol* 2018;**47**:760–70.
39. Zadro JR, Nilsen TIL, Shirley D, Amorim AB, Ferreira PH, Mork PJ. Parental chronic widespread pain and the association with chronic widespread pain in adult offspring: Family-linkage data from the Norwegian HUNT Study. *Eur J Pain* 2018;**22**:1485–93.
40. Clark DW, Okada Y, Moore KHS *et al.* Associations of autozygosity with a broad range of human phenotypes. *Nat Commun* 2019;**10**:4957.
41. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen WM. Robust relationship inference in genome-wide association studies. *Bioinformatics* 2010;**26**:2867–73.