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Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) – a national registry-based observational cohort with focus on care and treatment of key high-risk groups in Norway

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Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) – a national registry-based observational cohort with focus on care and treatment of key high-risk groups in Norway

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Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)

Abstract (word count: 299 (max. 300))

Purpose: The "Outcomes & Multi-morbidity in Type 2 Diabetes" (OMIT) is an observational registry-based cohort of Norwegian patients with type 2 diabetes (T2D) established to study high-risk groups often omitted from randomized clinical trials.

Participants: The OMIT cohort includes 57,572 patients with T2D identified via linkage of Norwegian Diabetes Register for Adults (NDR-A) and the Rogaland-Oslo-Salten-Akershus-Hordaland (ROSA4) study, both offering data on clinical patient characteristics and drug prescriptions. Subsequently these data are further linked to the Norwegian Prescription Database for dispensed medications, the Norwegian Population Register for data on death and migration, Statistics Norway for data on socio-economic factors and ethnicity and the Norwegian Directorate of Health for data on the general practices and clinical procedures involved in the care of cohort patients. OMIT offers large samples for key high-risk patient groups: 1) young-onset diabetes (T2D at age <40 years) (n = 6,510), 2) elderly (age >75 years) (n = 15,540), 3) non-Western ethnic minorities (n ~9,000) and 4) low socioeconomic status (n ~20,500).

Findings to date: On average, patient age and diabetes duration is 67.4 ±13.2 and 12.3 ±8.3 years, respectively, and mean HbA_{1c} for the whole cohort through the study period is 7.58±1.5%

(59.4±16.28 mmol/mol), mean BMI and blood pressure is 30.2±5.9 kg/m^2 and 135±16.1/78±9.8 mmHg, respectively. A total of 10.1% of the cohort has evidence of retinopathy, 21% with coronary heart disease and 6.7% has had a stroke.

Future plans: The OMIT cohort features 5,784 subjects with T2D in 2006, a number that has grown to 57,527 in 2019 and is expected to grow further via repeated linkages performed every third to fifth year. At the next wave of data collection, additional linkages to Norwegian Patient Registry and Norwegian Cause of Death Registry for data on registered diagnoses and causes of death, respectively, will be performed.

Strengths and limitations of this cohort

- The Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) cohort offers large sample size (between 2006 to 2019 including 57,527 patients) and over time growing regional representativeness.
- OMIT is produced from multiple linkages of high-quality Norwegian data-registries, with Norwegian Diabetes Register for Adults (NDR-A) as the primary source to identify patients, covering a wide range of key data-categories.

- OMIT is expected to grow further and to offer even more exhaustive data via repeated linkages performed every third to fifth year.

- OMIT may not be fully representative for Norwegian general practice, especially in the earlier years, as the majority of patients in the cohort are included from hospital outpatient clinics which are likely to differ from patients cared for only in general practice.

- There may be a risk of self-selection bias, especially for the earlier years, as those GPs willing to report data early on may have provided a higher level of care.

Introduction

Background

The prevalence of Type 2 diabetes (T2D) is increasing worldwide, and so is the burden of related vascular complications and death[1]. Diabetes is a major cause of cardiovascular disease, blindness[2], chronic kidney disease[3], diabetic foot ulcers[4] and limb amputations[5]. Beyond the immense reduction in quality of life, these complications lead to reduced labour market participation and inflict a considerable burden on the global economy[6].

Although timely and efficacious interventions can improve patient outcomes and reduce the economic burden[7], we often lack evidence for the effectiveness of current drug regimens in patients with greater needs as they are often omitted from clinical trials. Clinical guidelines from the European Association for the Study of Diabetes (EASD)[8], the American Diabetes Association[9] and Norwegian Directorate of Health[10] provide some guidance on how to manage diabetes treatments and disease control targets based on an individualized approach. However, a key weakness is the guidelines are based on results from trials where only 3.5–35.7% of patients in daily clinical practice would have been eligible to participate[11]. Therefore, the generated results from these trials may not be generalizable for the majority of patients, especially vulnerable groups such as 1) those with young onset diabetes (T2D prior to age 40),

2) elderly above 75 years, 3) ethnic minorities, and 4) patients with low socio-economic status. Moreover, the strategies suggested by the guidelines provide only a vague guidance as to how diabetes care should be customized and organized in a general practice setting and fail to deliver clear recommendations on how to address a broad range of key barriers to good disease control for vulnerable groups[12]. Consequently, we need more evidence to better understand the current unmet needs and evidence documenting the effectiveness, cost-effectiveness and safety of various treatments and clinical procedures in relation to how they may impact both disease control and harder disease outcomes in high-risk patients. As high-risk patients have proven difficult to include in prospective interventional trials, instead we see a great opportunity to employ non-interventional, observational data already present in various high-quality national registries.

The “Outcomes & Multi-morbidity in Type 2 Diabetes” (OMIT) cohort, which is based on multiple linkages between various Norwegian population-based registries, was established to support non-interventional observational studies of high-risk patients with T2D treated in general practice, in out-patient hospital clinics, or by shared care. The first wave of the OMIT cohort focus primarily on the following key high-risk groups: (1) young onset diabetes (YOD - T2D prior to age 40), (2) elderly patients (>75 years of age), (3) non-western ethnic minorities (i.e. non-

western immigrants excluding Eastern European immigrants), and (4) low socio-economic status (SES) patients. Low SES defined here as having only primary level education. The OMIT-cohort will also have data to support more refined SES-definitions accounting for personal and household income, as well as employment status (for those in working age).

OMIT research questions

Currently, we have three broad research questions:

(1) How does multi-morbidity interact with diabetes development, care and how is it related to intermediate and harder disease outcomes?

(2) How do newer anti-diabetic drugs perform in terms of real-life effectiveness (e.g. as opposed to drug efficacy, which can be measured only in randomized clinical trials), cost-effectiveness, safety and adherence in high-risk groups?

(3) What are the causes and effects of diabetes control variability on intermediate and harder disease outcomes, and how is the organization of diabetes care related to these outcomes?

For the intended investigation of key high-risk patient groups, we have further defined the following endpoints:

Primary endpoint: multi-morbidity measured according to the weighted prescription (Rx) Risk Comorbidity Index (RRCI), calculated based on recorded Anatomical Therapeutic Chemical (ATC) codes[13].

Secondary outcomes:

(1) Co-morbidity, ATC-code based estimates of key morbidity categories; (2) early onset diabetes; (3) mortality (4) diabetes-specific and macrovascular complications (5) drug adherence (6) drug treatment cascade (7) drug effectiveness and cost-effectiveness (8) polypharmacy and risk of potentially adverse drug interactions (9) quality of care/disease control (e.g. risk factor variability) (10) disability pension/sick leave.

Cohort description

Patient enrolment and sample size

OMIT eligible patients are identified from the Norwegian Diabetes Register for Adults (NDR-A) or the Rogaland-Oslo-Salten-Akershus-Hordaland (ROSA 4) study, covering the time-period from 2006 to 2019. Subsequently, these data sources are linked to the Norwegian Prescription Database for dispensed medications, the Norwegian Population Register for data on death and

migration, Statistics Norway for data on socio-economic factors and ethnicity and the Norwegian Directorate of Health for data on the general practices and clinical procedures involved in the care of cohort patients.

Figure 1 provides an overview of the different cohort-data sources, the time-periods covered with the first and second wave register linkages and the different data categories made available for the included cohort patients. First wave linkages involves data until December 31st 2019 whereas second wave linkages will extend covered time period until December 31st 2022 and supplement the cohort with additional data from the Norwegian Patient Registry and Norwegian Cause of Death Registry.

The NDR-A was established in 2005 with the aim of improving the quality of treatment of people with diabetes in Norway[14]. The registry has included out-patient hospital data since 2006, although reporting did not start until 2008. Primary care data has been included since 2009. Since then, the number of included patients in NDR-A has grown steadily. However, mainly due to requirements of written informed consent, enrolment was low in the early years, especially for people with T2D. In response, the ROSA 4 study was created to secure access to representative

data on patients with diabetes from diverse clinical settings. ROSA4 is a population-based cross-sectional survey conducted in 2015 (but based on data from the time period 2012-2014) that included people with T2D identified by general practitioners (GP) that agreed to participate. A total of 282 GPs, 77% of those invited, and 10,248 patients were enrolled[15].

As a natural extension of the past initiatives, the "Outcomes & Multi-morbidity in Type 2 Diabetes" (OMIT) project has now combined data from the NDR-A and ROSA4. OMIT will carry forward previous research efforts focusing on the quality of care for people with T2D in Norway, although this time with a dedicated focus on high-risk groups often omitted from randomized clinical trials (hence the acronym OMIT).

Figure 2 shows the number of OMIT cohort patients by source and year, as well as patient enrolment over time organized by hospital and primary care sources. **Figure 2** also shows that ROSA4 contributed data in the time-period 2012-2014, although some ROSA4 patients may also have been in the NDR-A prior to and after these years. The ROSA4 study comprises longitudinal laboratory and drug prescription data from 2012-2014 and cross-sectional data on other patient characteristics from 2014. When considering the overlap with the NDR-A, ROSA4 delivered an

additional 4,573 patients to the OMIT cohort. Going forward, we expect the cohort to grow further as a more GPs report to the register. Recent changes in national regulations have made it possible for national health registers to apply for inclusion of patients without informed consent if patients have not proactively put forward a request to be excluded[16]. In addition, The Norwegian Health Economics Administration (HELFO) has recently introduced a payment per registered patient to GPs who submit clinical data to the NDR-A. This is likely to accelerate GP reporting further. Consequently, the OMIT cohort is expected to grow to ~100,000 patients with T2D in 2022 (second wave linkages).

Between 2006 and 2019, a total of 57,527 individuals have been identified from the NDR-A and ROSA4, and included in OMIT. This includes 10,242 people within the ROSA4 study, 42,239 people with data in the NDR-A primary care database and 13,876 with data in the NDR-A hospital database. There is substantial overlap between the databases (**Figure 3**). For the high-risk groups, the current OMIT cohort includes data for about 6,500 YOD patients, 15,500 elderly (>75 years), about 9,000 non-western ethnic minority patients and 20,500 patients with primary education only.

Figure 4 illustrates development in the national coverage of the cohort via a series of maps, identifying the different counties of Norway. The fill colour is indicative of the county's total number of registered patients in OMIT, standardized to county population. In 2009, several counties had low coverage, such as the counties Sør-Trøndelag and Telemark, but this has improved over time to all counties having over 100 T2D patients per 100,000 residents included in the OMIT cohort in 2019, and several counties have over 1000 patients per 100,000. Although roughly one-third of GPs reported patients to the NDR–A in 2019, the OMIT-cohort at present only includes about 20% of the T2D population in Norway[17]. However, all counties are represented, and thus it offers good reliability when studying populations that may differ regionally.

Patient follow-up

The first wave linkages for the OMIT study included all data in NDR-A and ROSA4 up until the end of 2019. Patients are generally followed up at least once per year as one annual diabetes control is recommended as the minimum in general practice and GPs now receive a payment per patient for performing annual follow-up and reporting data to the NDR-A. In the current cohort, the median follow-up time between the first and final HbA1c measures is 2 years, with an

interquartile range (IQR) of 0 to 7 years and maximum of 14 years. The median number of visits is 6 (IQR 1 to 139). Despite having access to data from 2006 to 2009, the median follow-up reflects a large increase in first recordings in NDR-A in 2018 and 2019. To see clinical characteristics of current study participants, please see Table 1 (discussed more in detail in Chapter “Findings to date”).

Table 1. Total population characteristics and by separate data source (first wave linkages)

	Total (n = 57527) 2006 - 2019		ROSA4 (n = 10242) 2012 - 2014		NDR-A Primary Care (n = 42239) 2009 - 2019		NDR-A Hospital (n = 13876) 2006 - 2019	
	n (% missing)	mean (SD) or count (%)	n (% missing)	mean (SD) or count (%)	n (% missing)	mean (SD) or count (%)	n (% missing)	mean (SD) or count (%)
Sex- male	57527 (0.0%)	33367 (58.0%)	10242 (0.0%)	5626 (54.9%)	42239 (0.0%)	24211 (57.3%)	13876 (0.0%)	8620 (62.1%)
Age- years	57527 (0.0%)	67.4 (13.2)	10242 (0.0%)	69.8 (13.1)	42239 (0.0%)	68.3 (12.6)	13876 (0.0%)	63.0 (13.6)
Smoking- ever	52767 (8.3%)	28850 (54.7%)	7541 (26.4%)	3215 (42.6%)	37261 (11.8%)	20888 (56.1%)	8233 (40.7%)	5015 (60.9%)
Age at diagnosis- years	55303 (3.9%)	54.9 (12.9)	9769 (4.6%)	56.0 (12.9)	40755 (3.5%)	56.4 (12.4)	13492 (2.8%)	48.3 (12.6)
Diabetes duration- years	55303 (3.9%)	12.3 (8.3)	9769 (4.6%)	13.6 (7.0)	40755 (3.5%)	11.8 (8.0)	13492 (2.8%)	14.5 (9.1)
HbA1c- %	56092 (2.5%)	7.58 (1.5)	9931 (3.0%)	7.2 (1.3)	40689 (3.7%)	7.2 (1.2)	13775 (0.7%)	8.1 (1.7)
HbA1c- mmol/mol		59.38 (16.28)		54.79 (14.10)		55.36 (13.20)		65.38 (18.12)
BMI- kg/m^2	49983 (13.1%)	30.2 (5.9)	4662 (54.5%)	30.2 (6.0)	38255 (9.4%)	29.8 (5.9)	12635 (8.9%)	31.6 (6.2)
Systolic blood pressure- mmHg	52801 (8.2%)	135.0 (16.1)	8965 (12.5%)	135.0 (16.8)	38922 (7.9%)	135.0 (15.7)	11877 (14.4%)	135.0 (17.4)
Diastolic blood pressure- mmHg	52800 (8.2%)	78.0 (9.8)	8965 (12.5%)	78.0 (9.5)	38922 (7.9%)	77.6 (9.5)	11877 (14.4%)	78.1 (10.6)
Total cholesterol- mmol/L	50587 (12.1%)	4.6 (1.3)	9055 (11.6%)	4.7 (1.2)	35161 (16.8%)	4.5 (1.2)	13458 (3.0%)	4.7 (1.4)
HDL cholesterol- mmol/L	49114 (14.6%)	1.2 (0.4)	8776 (14.3%)	1.2 (0.4)	33773 (20.0%)	1.2 (0.4)	13414 (3.3%)	1.1 (0.3)
LDL cholesterol- mmol/L	49208 (14.5%)	2.7 (1.0)	8586 (16.1%)	2.8 (1.0)	34160 (19.1%)	2.7 (1.0)	13228 (4.7%)	2.7 (1.0)
Triglycerides- mmol/L	41715 (27.5%)	2.4 (2.8)	7335 (28.4%)	2.0 (1.8)	26594 (37.0%)	2.0 (1.7)	13240 (4.6%)	2.7 (3.5)
ACR*- mg/g	27253 (52.6%)	18.4 (75.4)	-	-	17301 (59.0%)	6.7 (33.0)	11033 (20.5%)	26.7 (93.7)
eGFR- ml/min/1.73^2	53142 (7.6%)	78.7 (30.8)	9701 (5.3%)	82.0 (24.3)	37488 (11.2%)	82.7 (25.1)	13665 (15.2%)	77.0 (32.9)
Retinopathy- yes	50638 (12.0%)	5138 (10.1%)	7570 (26.1%)	798 (10.5%)	38826 (8.1%)	2839 (7.3%)	11211 (19.2%)	2300 (20.5%)
Coronary heart disease- yes	54152 (5.9%)	11396 (21.0%)	10232 (0.1%)	2260 (22.1%)	40801 (3.4%)	8483 (20.8%)	11186 (19.4%)	2324 (20.8%)
Stroke- yes	53913 (6.3%)	3551 (6.7%)	10233 (0.1%)	758 (7.4%)	40601 (3.9%)	2563 (6.3%)	11124 (19.8%)	679 (6.1%)
Amputation- yes	52332 (9.0%)	489 (0.9%)	10233 (0.1%)	76 (0.7%)	38838 (8.1%)	214 (0.6%)	10207 (26.4%)	268 (2.6%)

Self-management course-completed	47467 (8.3%)	10326 (21.8%)	2257 (78%)	639 (28.3%)	39028 (7.6%)	9028 (23.1%)	11416 (17.7%)	2760 (24.2%)

*ACR values in this table are only derived from the NDR-A (primary care and hospital) records, excluding ROSA4, due to differences in reporting;
ACR = albumin creatinine ratio, BMI = body mass index, eGFR = estimated glomerular filtration rate, HDL = high density lipoprotein, LDL = low density lipoprotein, NDR-A = Norwegian Diabetes Register-Adult, ROSA4 = Rogaland Hordaland Oslo Salten Akershus 4 Study, SD = standard deviation
NB: Patients may be registered in multiple sources. The total, however, indicates the overall mean for identified 57,527 individual patients.

Future patient enrolment and sample sizes

In the years to come we expect the NDR-A, e.g. the primary source for identifying and including patients into OMIT, to include recurring annual data for a growing proportion of the cohort-patients as more GPs are likely to report. Further, the number of recorded measurements per year, especially concerning HbA1c, blood pressure and drug prescriptions, are likely to increase as GPs tend to follow-up their patients more frequently as compared to the out-patient hospital clinics. As already stated, to strengthen the cohort, we therefore plan to replicate the linkages with new waves of data every three to five years to increase the number of patients with T2D included in the OMIT cohort. Thus, we expect the NDR-A to grow, with 15 000 new patients, as observed during 2019, to about 30 000 new patients annually over the next five years. As a result, we expect the OMIT cohort to grow to approximately 100,000 and 150,000 patients in 2022 (second wave linkages) and 2025 (third wave linkages), respectively. In addition, already with the second wave, it is planned for the OMIT cohort to be further linked with the Norwegian Patient Registry and the Norwegian Cause of Death Registry. This will further strengthen the

comprehensiveness of the cohort and prove solid ground for future studies focusing on mortality related outcomes.

Data sources and categories

NDR-A and ROSA4: Data gathered from NDR-A and ROSA4 databases include a wide array of demographic and clinical data. These data include year of birth, sex and regional location, diabetes variables including year of diagnosis and HbA1c measures, as well as blood pressure and lipid measurements and prescribed medications. We have also collected important vascular outcomes such as retinopathy, cardiovascular disease, nephropathy and markers of neuropathy that include evidence of foot ulcers, monofilament foot examinations and pulse testing. **Table 1** provides an overview of some of the important clinical variables collected from NDR-A and ROSA4.

Statistics Norway (SSB): Data gathered from Statistics Norway mainly cover socio-economic factors, including education, disability income, sick-leave and country of birth.

Norwegian Population Register (NPR): The data from NPR will provide detailed information on migration of the patients within the study, including dates for immigration and/or emigration and death.

Norwegian Prescription Database (NorPD): Data from the NorPD represent all dispensed prescriptions by date and ATC-codes for each participant. The OMIT cohort also obtains date of death from NorPD.

Further, based on ATC codes we will construct and validate an ATC-code based multi-morbidity score[13] , which will then serve as an individual measure applicable as either an exposure or an outcome in subsequent research studies.

Norwegian Directorate of Health: The Norwegian Directorate of Health manages several national registers, including the medical claims register (KUHR) and the Health Personnel Register (HPR), from which we will receive data on GPs and features of their clinical practices. This includes patient list size, waiting list size, patient turnover data and demographics. GP characteristics include specialist status and whether the GP is salaried or self-employed, as well as an overview of the procedure-related payments and diagnoses recorded by the GP, enabling analyses of health economic outcomes.

Findings to date

In 2019, the average age of the OMIT cohort was 67.4±13.2 years with an average T2D duration of 12.3±8.3 years (**Table 1**). The mean HbA1c for the whole cohort through the study period was 7.58±1.5% (59.4±16.28 mmol/mol), BMI was 30.2±5.9 kg/m^2 and blood pressure 135±16.1/78±9.8

mmHg. A total of 10.1% of the cohort had evidence of retinopathy, 21% with coronary heart disease and 6.7% had had a stroke. Missing data varied greatly depending on the variable, with only 2.5% of the cohort missing HbA1c measures, while up to 52.6% were missing urinary albumin creatinine ratio (ACR).

Table 1 shows only the main diabetes related variables by source, and how data from different sources can be mutually supplementary to reduce the impact of missing data obtained from a single source. For example, 14.4% were missing blood pressure measurements from NDR-A hospital records, but due to the higher coverage by the NDR-A primary care records, only 8.2% of the whole cohort have missing blood pressure readings. Even though urinary ACR currently has a high amount of missing data, we will have the advantage of a large sample size in addition to a broad range of other co-variables (including estimates of glomerular filtration rate (eGFR) (calculated by use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations using serum creatinine measures[18])) which will allow imputation for missing ACR values.

The ROSA4 study, a seminal part of OMIT, has already published many studies related to T2D care in Norway, including findings that non-Western ethnic minorities are diagnosed with T2D at an earlier age than Westerners and are less likely to achieve target HbA1c measures[19]. An early

study demonstrated modest improvements in diabetes related risk markers from 2005 to 2014 in general practice, including HbA1c, blood pressure and lipids, but revealed suboptimal screening for microvascular complications, such as nephopathy[15]. Another ROSA4 study indicated that point-of-care HbA1c testing in general practice was linked to better glycaemic regulation in patients with T2D[20]. Finally, ROSA4 has reported that GP adherence to recommended standard follow-up procedures in T2D was related to both clinic structure and workload[21].

Now that we have expanded the ROSA4 study, we are optimistic the OMIT cohort can further drive the work to enhance our knowledge about how we treat and care for patients with T2D in Norway. This work will position us to put forward concrete and tangible evidence-based recommendations on how diabetes care may be improved, with a special attention to high-risk patients.

Strengths and limitations

Strengths

The OMIT cohort is the first dedicated T2D cohort in Norway constructed from high-quality national registry data that includes patients from all counties, with increasing representativeness over time. Further, OMIT provides separate data from both out-patient clinics and general

practices which enables studies of potential differences between these two patient populations. OMIT will support detailed analyses that will generate both nationally generalizable as well as internationally relevant findings. This surpasses the ability of studies such as HUNT and Tromsø Study, both of which are regionally restricted, rely partially on self-reported diabetes diagnoses and have a lower sample size of patients with T2D[21]. Most OMIT data are longitudinal, which allows us to assess exposures at a time point prior to the defined outcomes. Also, OMIT will provide a basis for studying causes and effects of multi-morbidity rather than only traditional risk factors (e.g. hypertension, hyperglycaemia, hyperlipidaemia etc.). We currently have an extensive dataset that provides us with a full description of clinical features, socio-demographics, economy and ethnicity, drug prescriptions and drug retrievals, delivered care and treatment processes, and organizational factors including collaborations between primary and specialist care. Together these data provide a strong basis for assessing possible relations between all the defined exposures and outcomes and to correct for a multitude of confounders. In order to explore potential causal factors, we will draw Directed Acyclic Graphs (DAGs) prior to analyses to identify true confounders to be adjusted for, in line with statistical methods developed to support causal inference in observational data.

Limitations

In this first wave of linkage, the majority of patients in the cohort are included from hospital outpatient clinics which are likely to differ from patients cared for only in general practice, a condition reflected by a mean HbA1c for the whole cohort as high as 7.58% (59.4±16.28 mmol/mol). Further, in the current OMIT cohort there may be a risk of selection bias, particularly in the earlier years in the NDR-A data reported by GPs, as those willing to participate early on may have provided a higher level of care. This type of bias can mean there is lower external validity of primary care NDR-A data reported earlier. We plan to assess the overall representativeness of these data by use of the ROSA4-population which is considered more representative for Norwegian general practice. Some variables have high levels of missing data, and follow-up time-periods vary between data sources and within patients. Thus, it may be relevant to perform analysis of potential selection bias due to self-selection and missing data.

Data Availability Statement

All OMIT data are stored and analysed on the platform for safe storage of sensitive data (TSD) at the University of Oslo until 2035. In support of collaborative research projects, access can be granted after approval by the OMIT-study group, the Regional Committee for Medical and Health

Research Ethics and the data owner at the University of Oslo. Project requests can be directed to Esben Selmer Buhl at the Department of General Practice, Institute of Health and Society, University of Oslo (email: e.s.buhl@medisin.uio.no)

Further details

Funding

The first phase of linkages has been funded by the University of Oslo. Currently, senior researchers and one postdoctoral position (Western Norway University of Applied Sciences (HVL), Norway) are funded by their home institutions (for senior researchers: see author affiliation list). The cohort is also funded by The Norwegian Diabetes Association (Diabetesforbundet) and the Norwegian Research Fund for General Practice (Allmennmedisinsk forskningsfond), with the latter also funding one PhD-student (University of Oslo (UiO), Norway).

Ethics and ethics approval

The project has obtained ethical approval from Regional Committees for Medical Research Ethics - South East Norway (REC South East (Ref# 74012)) and is approved by the Data Protection Official/Officer at UiO. Data linkage began in mid-2020 for the years 2006-2019. After the final linkages of data from all registers, all researchers are not in any way be able to identify individual patients. We have reduced the number of categories for variables (data minimization)

to secure a sufficient number in each cell so that patients cannot be retrospectively identified. Individual researchers will only have access to variables relevant for their research questions, and only after granted approval from REC South East.

Patient and Public Involvement

The OMIT-study has received a letter of endorsement from the Norwegian Diabetes Association in addition to financial support, and key senior researchers from the OMIT-study group, including Prof. Emeritus Anne Karen Jenum, over the years with the ROSA4-study have had a long-standing close collaboration with Norwegian Diabetes Association, which we aspire to continue with the OMIT-initiative.

To secure that the current research project will result in tangible and quantifiable improvements in the clinical care of high-risk patients with T2D, in alignment with patient preferences and identified unmet needs, we have the identified the following key strategic objectives and the related target stakeholder and tactics:

Strategic objective: **Strengthen GP diabetes education**.

- *Target stakeholder*: Norwegian Medical Association (Den Norske Legeforening (DNLF)) and Association of General Practitioners (*Allmennlegeforeningen*) – later on other Nordic Medical Associations may also be relevant.
- *Tactics*: Ensure a dedicated class with focus on high-risk patients is incorporated into the annual pre- and post-gradual national courses in diabetes.

Strategic objective: **Improve clinical guidelines for key high-risk patients.**

- *Target stakeholder*: Norwegian guideline author group.
- *Tactics*: Translate key research findings into concrete suggestions on how to individualize guidelines for high-risk patients and on how different drug regimens may help solve key clinical issues such as non-adherence, therapeutic inertia and disease control variability in high-risk patients.

Strategic objective: **Secure high-risk patients access to innovation (e.g. reimbursement).**

- *Target stakeholder:* The Norwegian Medicines Agency (Legemiddelverket (LMV)) and the Norwegian Directorate of Health (Helsedirektoratet).
- *Tactics*: Identify and share patient subgroups with most attractive cost-benefit-ratio.

Strategic objective: **Enhance patient competences and empowerment.**

- *Target stakeholder:* Norwegian Diabetes Association (Diabetes Forbundet).
- *Tactics:* Norwegian Diabetes Association has written a letter of endorsement and granted financial resources to support the OMIT-initiative. Going forward, in close dialogue with the Norwegian Diabetes Association, the OMIT-study group will ensure key research findings and key takeaways with relevance for patients will be communicated to patients, using both the webpage and the membership magazine of Norwegian Diabetes Association.

Strategic objective: **Improve political willingness to invest in high-risk patients.**

- *Target stakeholders:* Public media, Ministry of Health and Care Services and other political key decision makers.
- *Tactics:* Disseminate data and key takeaways related to current unmet needs in diabetes care but also communicate key conclusions regarding the effectiveness and cost-effectiveness of various treatments and interventions to build public and political awareness of inequality in diabetes outcomes and use evidence to shift focus from short-term budget impact to impact in the long-term on compiled disease life-cycle costs.

Strategic objective: **Ensure generated hypotheses are tested in prospective interventional studies.**

- *Target stakeholders:* Diabetes researchers in Norway and abroad and researchers involved in Norwegian general practice research network.
- *Tactics:* Ensure scientific data are presented at national and international scientific conferences and published in high-impact peer reviewed journals. In addition, identify hypotheses relevant to test in future prospective and interventional studies.

With this strategic approach, we aspire that the OMIT-project will help increase public awareness about unmet needs in current care, support patient empowerment by strengthening patient organization competences, influence policy makers to perform relevant and cost-effective investments, improve national guidelines and facilitate that the right patients get access to right treatments at the right time.

Competing interests

All authors have filled out and signed a “Disclosure of potential conflicts of interests”-form which can be reproduced upon request. E.S. Buhl is a previous employee of Novo Nordisk (2011-16) and has offered medical consulting and lectures to Novo Nordisk, Sanofi Aventis and MundiPharma. J.G. Cooper has received lecturing fees from Novo Nordisk, Sanofi Aventis, Eli Lilly, AstraZeneca, GSK. All other authors declare no conflicts of interests.

Author contributions

Together Dr. E.S. Buhl and Prof. Emeritus A.K. Jenum have initiated and driven the work related to drafting the overall OMIT research protocol, to applying for local ethics committee approval and to the process of performing the register linkages. Dr. E.S. Buhl is the primary investigator (P.I.) on the OMIT-cohort study and Prof. M. M. Iversen has recently succeeded Prof. Emeritus Dr. A.K. Jenum in the role as Co-P.I.

Dr. K. Nøkleby, Dr. T. J. Berg, Prof. T. Iversen, Prof. T Hagen, Dr. J. Cooper, Prof. S. Sandberg and DrMsc. K. F. Løvaas have also provided substantial inputs to the overall OMIT-research protocol. After local ethics committee approval of the study-protocol, Dr. K. R. Richardsen, Prof. R. M. Nilsen and Prof. M. M. Iversen have joined the OMIT-study group, and co-P.I. Prof. M. M. Iversen has contributed substantially with the refinement of some of the research questions related to the protocol as well as to the strategic planning of the overall project. The first three Ph.D/Post.Doc.-research projects, out of six planned for the time being, originating from the protocol are in the process of being executed as a 1) PhD.-project focusing on complications in YOD patients (Dr. K. Tibballs based at University of Oslo (UiO) with Dr. E.S. Buhl as supervisor), 2) as a Post.Doc.-project assessing quality of care in elderly with T2D (Dr. R. B. Strandberg based at Western Norway University of Applied Sciences (HVL) with Prof. M.M. Iversen as

supervisor) and 3) a Post.Doc.-project focusing on real-life drug effectiveness in YOD and elderly patients with T2D (candidate to be determined).

Dr. R. B. Forster has worked with the initial analyses and quality check of the data files and has first authored this cohort paper. All other researchers mentioned above each have contributed significantly with the writing and review of this manuscript with last author and P.I. Dr. E. S. Buhl taking the role as corresponding author.

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Figure legends

Figure 1.

Overview of OMIT cohort construction, covered time-periods and overall data categories and co-variables.

Figure 2.

Number of OMIT cohort patients by source and year (first wave linkages).

The bars shown above only indicate the number of OMIT-patients reported to the NDR-A registry. Although reporting to the NDR-A registry did not start until 2008, please note that the current cohort still includes some outpatient hospital data for the years 2006-2007. The green and transparent bars, placed in a front position, reflect the number of patients by year reported to NDR-A by hospital clinics, whereas violet bars, placed behind the green transparent bars, give the number of patients reported by year to the NDR-A by GPs. For the years 2012-14, please note that the ROSA4-data base contributed with additional 4,573 GP patients to the cohort which, however, are not accounted for in the shown violet bars.

Figure 3.

Venn diagram of overlap for total number of registered patients in OMIT cohort, with the first wave linkages, from the three different sources.

NB: When accounting for those overlaps, please note that the first wave cohort has enrolled 57,527 individual patients with type 2 diabetes.

Figure 4.

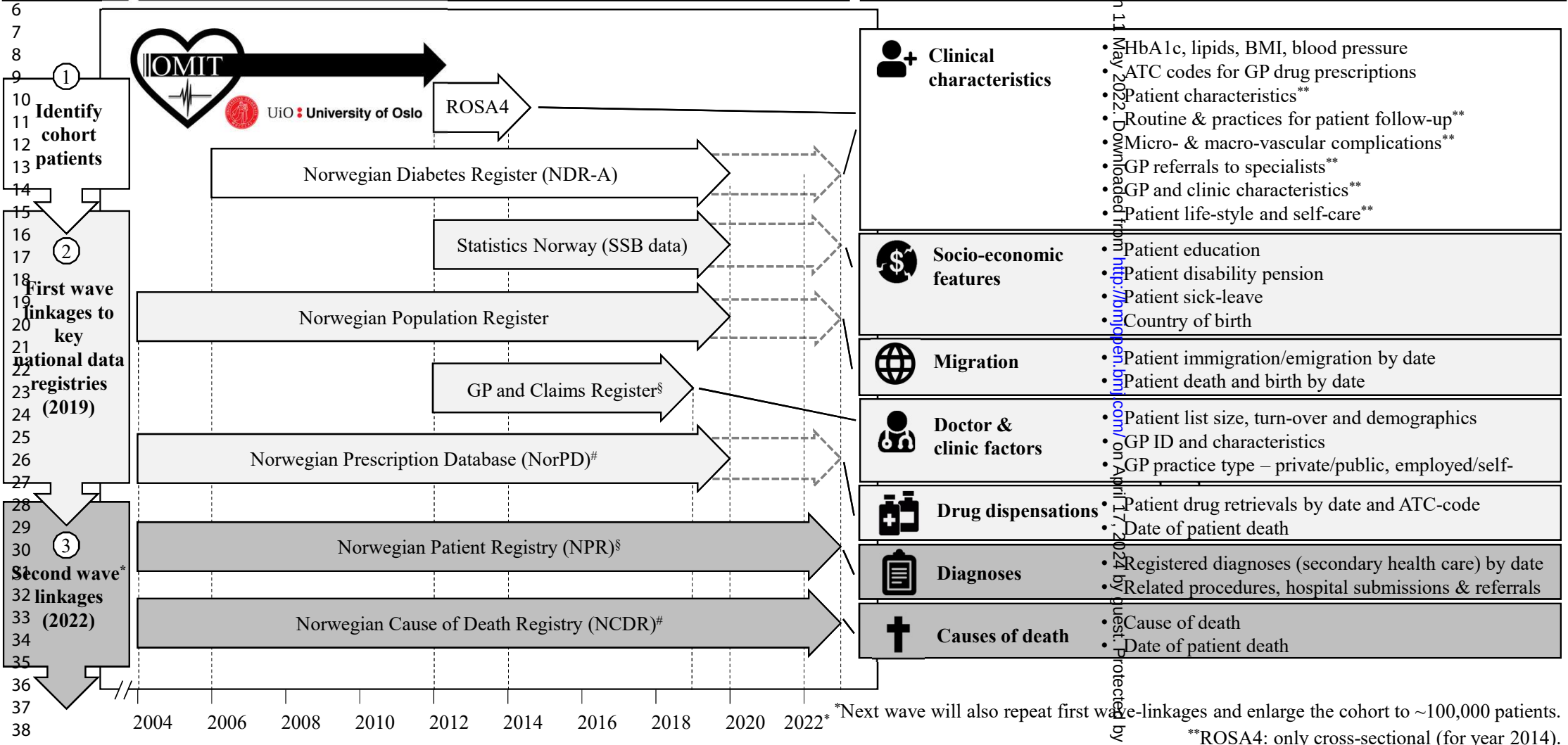
Number of registered OMIT patients by year by county, standardised to total county population.

County legend, e.g. ISO-codes: 1. Østfold; 2 Akershus; 3 Oslo; 4 Hedmark; 5 Oppland; 6 Buskerud; 7 Vestfold; 8 Telemark; 9 Aust-Agder; 10 Vest-Agder; 11 Rogaland; 12 Hordaland; 14 Sogn og Fjordane; 15 Møre og Romsdal; 16 Sør-Trøndelag*; 17 Nord-Trøndelag*; 18 Troms; 20 Finnmark.

* In 2019 Nør- and Sør-Trøndeag were combined in to a single county, Tøndelag, ISO-code 50.

§ Regions that contributed to data in the ROSA4 study in 2014: Rogaland, Oslo, Salten - a region in Nordland - , Akershus and Hordaland.

Figure 1
Process to build OMIT



*Next wave will also repeat first wave-linkages and enlarge the cohort to ~100,000 patients.
**ROSA4: only cross-sectional (for year 2014).
§Data source managed by Norwegian Directorate of Health.
#Data source managed by Norwegian Institute of Public Health.

Source: OMIT Cohort Research Group

Figure 2

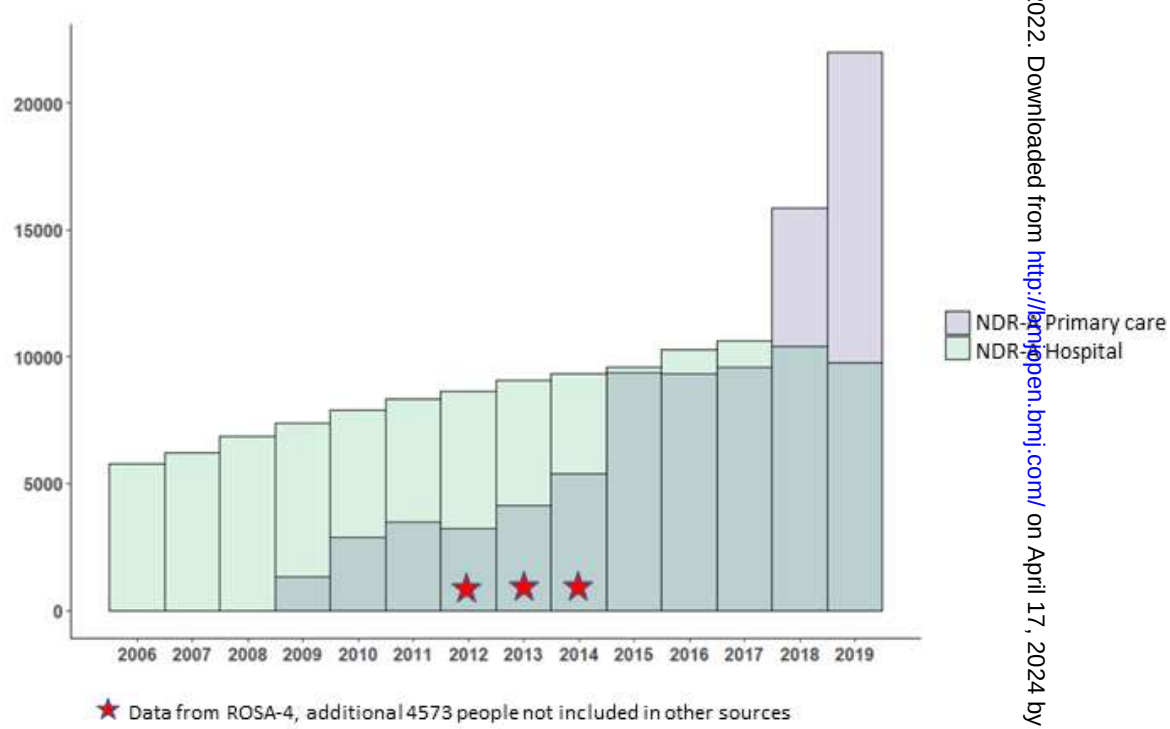


Figure 3

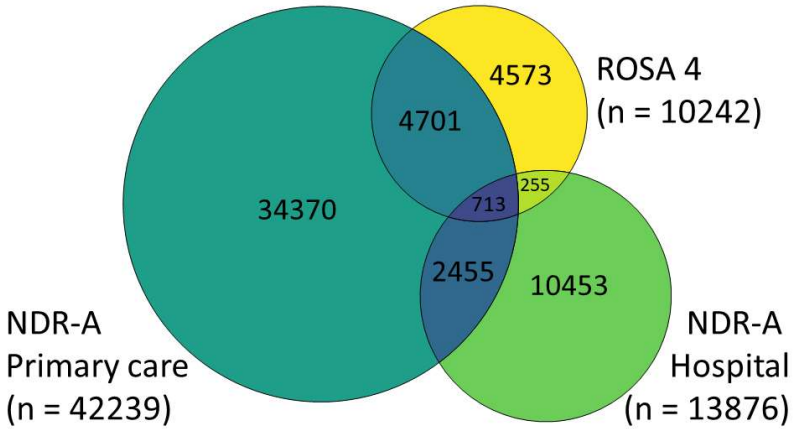
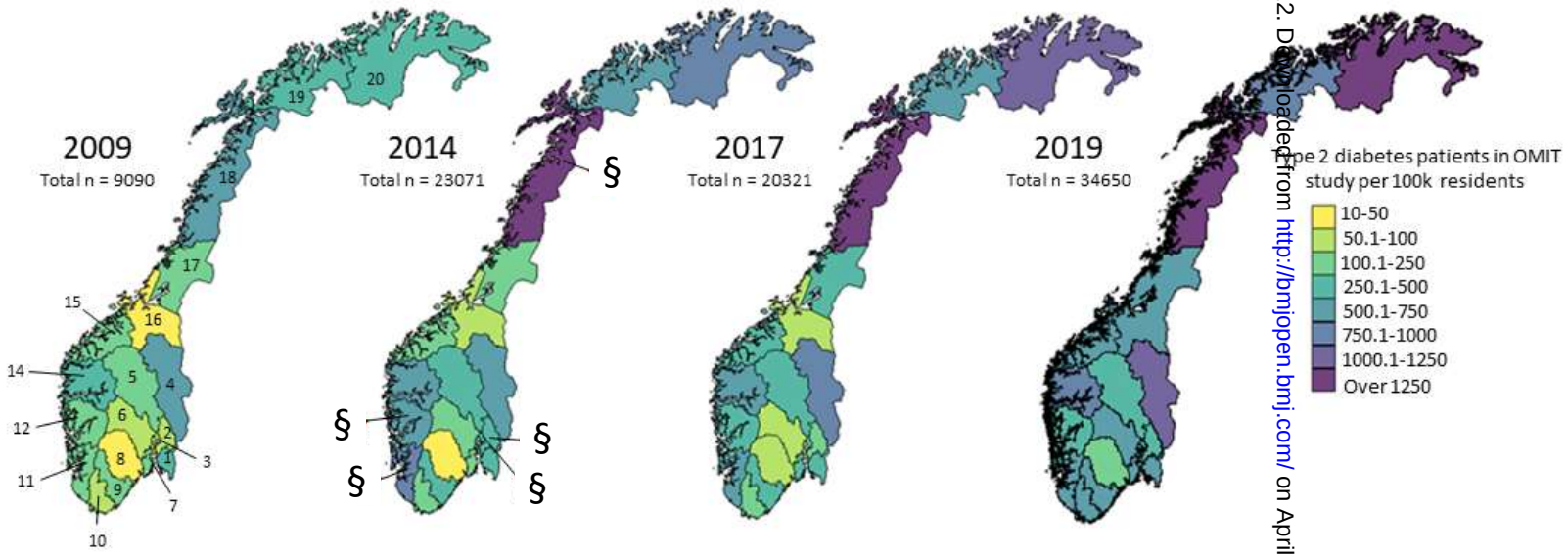


Figure 4



Logo for the OMIT cohort

338x190mm (96 x 96 DPI)

BMJ Open

Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) – a national registry-based observational cohort with focus on care and treatment of key high-risk groups in Norway

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V5 19/12/2021

Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) – a national registry-based observational cohort with focus on care and treatment of key high-risk groups in Norway

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V5 19/12/2021

Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)

Abstract (word count: 291 (max. 300))

Purpose: The "Outcomes & Multi-morbidity in Type 2 Diabetes" (OMIT) is an observational registry-based cohort of Norwegian patients with type 2 diabetes (T2D) established to study high-risk groups often omitted from randomized clinical trials.

Participants: The OMIT cohort includes 57,572 patients with T2D identified via linkage of Norwegian Diabetes Register for Adults (NDR-A) and the Rogaland-Oslo-Salten-Akershus-Hordaland (ROSA4) study, both offering data on clinical patient characteristics and drug prescriptions. Subsequently these data are further linked to the Norwegian Prescription Database for dispensed medications, the Norwegian Population Register for data on death and migration, Statistics Norway for data on socio-economic factors and ethnicity and the Norwegian Directorate of Health for data on the general practices and clinical procedures involved in the care of cohort patients. OMIT offers large samples for key high-risk patient groups: 1) young-onset diabetes (T2D at age <40 years) (n = 6,510), 2) elderly (age >75 years) (n = 15,540), 3) non-Western ethnic minorities (n ~9,000) and 4) low socioeconomic status (n ~20,500).

Findings to date: On average, patient age and diabetes duration is 67.4 ±13.2 and 12.3 ±8.3 years, respectively, and mean HbA_{1c} for the whole cohort through the study period is 7.6±1.5%

(59.4±16.3 mmol/mol), mean BMI and blood pressure is 30.2±5.9 kg/m^2 and 135±16.1/78±9.8 mmHg, respectively. Prevalence of retinopathy, coronary heart disease and stroke is 10.1%, 21% and 6.7%, respectively.

Future plans: The OMIT cohort features 5,784 subjects with T2D in 2006, a number that has grown to 57,527 in 2019 and is expected to grow further via repeated linkages performed every third to fifth year. At the next wave of data collection, additional linkages to Norwegian Patient Registry and Norwegian Cause of Death Registry for data on registered diagnoses and causes of death, respectively, will be performed.

Strengths and limitations of this cohort

- The Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) cohort offers large sample size (between 2006 to 2019 including 57,527 patients) and over time growing regional representativeness.
- OMIT is produced from multiple linkages of high-quality Norwegian data-registries, with Norwegian Diabetes Register for Adults (NDR-A) as the primary source to identify patients, covering a wide range of key data-categories.

- OMIT is expected to grow further and to offer even more exhaustive data via repeated linkages performed every third to fifth year.

- OMIT may not be fully representative for Norwegian general practice, especially in the earlier years, as many of the patients then were included from hospital outpatient clinics and are likely to differ from patients cared for only in general practice.

- There may be a risk of self-selection bias, especially for the earlier years, as those GPs willing to report data early on may have provided a higher level of care.

Introduction

Background

The prevalence of Type 2 diabetes (T2D) is increasing worldwide, and so is the burden of related vascular complications and death[1]. Diabetes is a major cause of cardiovascular disease, blindness[2], chronic kidney disease[3], diabetic foot ulcers[4] and limb amputations[5]. Beyond the immense reduction in quality of life, these complications lead to reduced labour market participation and inflict a considerable burden on the global economy[6].

Although timely and efficacious interventions can improve patient outcomes and reduce the economic burden[7], the evidence for current drug regimens is often limited in patients with greater needs as they are often omitted from clinical trials. Clinical guidelines from the European Association for the Study of Diabetes (EASD)[8], the American Diabetes Association[9] and Norwegian Directorate of Health[10] provide some guidance on how to manage diabetes treatments and disease control targets based on an individualized approach. However, a key weakness is the guidelines are based on results from trials where only 3.5–35.7% of patients in daily clinical practice would have been eligible to participate[11]. Therefore, the generated results from these trials may not be generalizable for the majority of patients, especially vulnerable groups such as 1) those with young onset diabetes (T2D prior to age 40), 2) elderly above 75

years, 3) ethnic minorities, and 4) patients with low socio-economic status. Moreover, the strategies suggested by the guidelines provide only a vague guidance as to how diabetes care should be customized and organized in a general practice setting and fail to deliver clear recommendations on how to address a broad range of key barriers to good disease control for vulnerable groups[12]. Consequently, we need more evidence to better understand the current unmet needs and evidence documenting the effectiveness, cost-effectiveness and safety of various treatments and clinical procedures in relation to how they may impact both disease control and harder disease outcomes in high-risk patients. As high-risk patients have proven difficult to include in prospective interventional trials, instead we see a great opportunity to employ non-interventional, observational data already present in various high-quality national registries.

The “Outcomes & Multi-morbidity in Type 2 Diabetes” (OMIT) cohort, which is based on multiple linkages between various Norwegian population-based registries, was established to support non-interventional observational studies of high-risk patients with T2D treated in general practice, in outpatient hospital clinics, or by shared care. The first wave of the OMIT cohort focus primarily on the following key high-risk groups: (1) young onset diabetes (YOD - T2D prior to age 40), (2) elderly patients (>75 years of age), (3) non-western ethnic minorities (i.e. non-western

immigrants excluding Eastern European immigrants), and (4) low socio-economic status (SES) patients. Low SES defined here as having only primary level education. The OMIT-cohort will also have data to support more refined SES-definitions accounting for personal and household income, as well as employment status (for those in working age).

OMIT research questions

Currently, we have three broad research questions:

(1) How does multi-morbidity interact with diabetes development and care, and how is it related to intermediate (e.g HbA_{1c}, LDL and/or blood pressure) and harder disease outcomes (e.g. diabetes-specific complications and/or death)?

(2) How do newer anti-diabetic drugs perform in terms of real-life effectiveness (e.g. as opposed to drug efficacy, which can be measured only in randomized clinical trials), cost-effectiveness, safety and adherence in high-risk groups?

(3) What are the causes and effects of diabetes control variability on intermediate and harder disease outcomes and how is the organization of diabetes care related to these outcomes?

To answer the overall research questions, we have planned several individual studies to investigate the following outcomes in key high-risk patient groups (ranked in descending order according to number of planned studies):

- Primary outcomes: (1) Multi-morbidity, (2) diabetes-specific complications, (3) mortality/survival, (4) variability in disease control (e.g. variability in relation to intermediate disease outcomes), (5) drug effectiveness and cost-effectiveness, (6) drug adherence and (7) YOD.
- Secondary outcomes: (1) ATC-code based co-morbidity, (2) mortality, (3) diabetes-specific complications, (4) drug adherence, (5) drug treatment cascade, (6) drug effectiveness and cost-effectiveness, (7) polypharmacy and risk of potentially adverse drug interactions, (8) variability in disease control (e.g. variability in relation to intermediate disease outcomes), (9) YOD and (10) disability pension/sick leave.

Cohort description

Data sources and categories

NDR-A and ROSA4: The NDR-A and ROSA4 databases include a wide array of demographic and clinical data. These data include year of birth, sex and regional location, diabetes variables

including year of diagnosis and HbA_{1c} measures, as well as blood pressure and lipid measurements and prescribed medications. We have also collected important vascular outcomes such as retinopathy, cardiovascular disease, nephropathy and markers of neuropathy that include evidence of foot ulcers, monofilament foot examinations and pulse testing. **Table 1** provides an overview of some of the important clinical variables collected from NDR-A and ROSA4.

Statistics Norway (SSB): Data gathered from Statistics Norway mainly cover socio-economic factors, including education, disability income, sick-leave and country of birth.

Norwegian Population Register (NPR): This register will provide detailed information on migration of the patients within the study, including dates for immigration and/or emigration and death.

Norwegian Prescription Database (NorPD): NorPD data represent all dispensed prescriptions by date and ATC-codes for each participant. The OMIT cohort also obtains date of death from NorPD.

Further, based on ATC codes we will construct an ATC-code based multi-morbidity score[13], which will be validated based on its ability to predict 1- and 5-year mortality. The score will then

serve as an individual measure applicable as either an exposure or an outcome in subsequent research studies.

Norwegian Directorate of Health: The Norwegian Directorate of Health manages several national registers, including the medical claims register (KUHR) and the Health Personnel Register (HPR), from which we will receive data on GPs and features of their clinical practices. This includes patient list size, waiting list size, patient turnover data and demographics. GP characteristics include specialist status and whether the GP is salaried or self-employed, as well as an overview of the procedure-related payments and diagnoses recorded by the GP, enabling analyses of health economic outcomes.

Patient enrolment and sample size

The eligibility criteria for the OMIT cohort are all T2D patients over 18 years. All patients are identified from the Norwegian Diabetes Register for Adults (NDR-A) or the Rogaland-Oslo-Salten-Akershus-Hordaland (ROSA 4) study, covering the time-period from 2006 to 2019. Subsequently, these data sources are linked to the Norwegian Prescription Database for dispensed medications, the Norwegian Population Register for data on death and migration, Statistics Norway for data on socio-economic factors and ethnicity and the Norwegian

Directorate of Health for data on the general practices and clinical procedures involved in the care of cohort patients.

Figure 1 shows the different cohort-data sources, the time-periods covered with the first and second wave register linkages and the different data categories made available for the included cohort patients. For more details, please see chapter “Data sources and categories” below. First wave linkages involves data until December 31st 2019 whereas second wave linkages will extend covered time period until December 31st 2022 and supplement the cohort with additional data from the Norwegian Patient Registry and Norwegian Cause of Death Registry.

The NDR-A was established in 2005 with the aim of improving the quality of treatment of people with diabetes in Norway[14]. The registry has included outpatient hospital data since 2006, although reporting did not start until 2008. Primary care data has been included since 2009. Since then, the number of included patients in NDR-A has grown steadily. However, mainly due to requirements of written informed consent, enrolment was low in the early years, especially for people with T2D. In response, the ROSA 4 study was created to secure access to representative data on patients with diabetes from diverse clinical settings. ROSA4 is a population-based cross-sectional survey conducted in 2015 (but based on data from the time period 2012-2014) that included 10,248 people with T2D identified by 282 general practitioners (GPs) [15].

As an extension of the past initiatives, the "Outcomes & Multi-morbidity in Type 2 Diabetes" (OMIT) project has now combined data from the NDR-A and ROSA4. OMIT will carry forward previous research efforts focusing on the quality of care for people with T2D in Norway, although this time with a dedicated focus on high-risk groups often omitted from randomized clinical trials (hence the acronym OMIT).

Figure 2 shows the number of OMIT cohort patients by source and year, as well as patient enrolment over time organized by hospital and primary care sources. **Figure 2** also shows that ROSA4 contributed data in the time-period 2012-2014, although some ROSA4 patients may also have been in the NDR-A prior to and after these years. The ROSA4 study comprises longitudinal laboratory and drug prescription data from 2012-2014 and cross-sectional data on other patient characteristics from 2014. When considering the overlap with the NDR-A, ROSA4 delivered an additional 4,573 patients to the OMIT cohort. Going forward, we expect the cohort to grow further as a more GPs report to the register. Recent changes in national regulations have made it possible for national health registers to apply for inclusion of patients without informed consent if patients have not proactively put forward a request to be excluded[16]. In addition, The Norwegian Health Economics Administration (HELFO) has recently introduced a payments to GPs who submit data to the NDR-A. This is likely to accelerate GP reporting further.

Consequently, the OMIT cohort is expected to grow to ~100,000 patients with T2D in 2022 (second wave linkages).

Between 2006 and 2019, a total of 57,527 individuals have been included in OMIT. Hereof 10,242 patients from the ROSA4 study, 42,239 from the NDR-A primary care database and 13,876 from the NDR-A hospital database. There is substantial overlap between the databases (**Figure 3**). For the high-risk groups, the current cohort includes data for about 6,500 YOD patients, 15,500 elderly (>75 years), about 9,000 non-western ethnic minority patients, e.g. predominantly South and East Asian or African ethnical background, and 20,500 patients with primary education only.

Figure 4 illustrates development in the national coverage of the cohort via a series of maps, identifying the different counties of Norway. The fill colour indicates the county's total number of registered patients in OMIT, standardized to county population. In 2009, several counties had low coverage, such as the counties Sør-Trøndelag and Telemark, but this has improved over time to all counties having over 100 T2D patients per 100,000 residents included in the OMIT cohort in 2019, and several counties have over 1000 patients per 100,000. Although roughly one-third of GPs reported patients to the NDR–A in 2019, the OMIT-cohort at present only

includes about 20% of the T2D population in Norway[17]. However, all counties are represented, and thus it offers good reliability when studying populations that may differ regionally.

Patient follow-up

The first wave linkages included all data in NDR-A and ROSA4 up until the end of 2019. Patients are generally followed up at least once per year as one annual diabetes control is recommended as the minimum in general practice and GPs now receive a payment per patient for performing annual follow-up and reporting data to the NDR-A. In the current cohort, the median follow-up time between the first and final HbA_{1c} measures is 2 years, with an interquartile range (IQR) of 0 to 7 years and maximum of 14 years. The median number of visits is 6 (IQR 1 to 139). Despite having access to data from 2006 to 2009, the median follow-up reflects a large increase in first recordings in NDR-A in 2018 and 2019. To see clinical characteristics of current study participants, please see Table 1 (for more details, please see Chapter “Findings to date”).

Future patient enrolment and sample sizes

Going forward, we expect the NDR-A, e.g. the primary source for including patients into OMIT, to include recurring annual data for a growing proportion of the cohort-patients as more GPs are likely to report. Further, the number of recorded measurements per year, especially concerning HbA_{1c}, blood pressure and drug prescriptions, are likely to increase as GPs tend to follow-up

their patients more frequently as compared to the outpatient hospital clinics. As already stated, to increase the sample size of the cohort, we therefore plan to replicate the linkages with new waves of data every three to five years. Thus, we expect the NDR-A to grow, with 15 000 new patients, as observed during 2019, to about 30 000 new patients annually over the next five years. As a result, we expect the OMIT cohort to increase to approximately 100,000 and 150,000 patients in 2022 (second wave linkages) and 2025 (third wave linkages), respectively. In addition, already with the second wave, it is planned for the OMIT cohort to be further linked with the Norwegian Patient Registry and the Norwegian Cause of Death Registry. This will further strengthen the comprehensiveness of the cohort and prove solid ground for future studies focusing on mortality related outcomes.

Findings to date

In 2019, the average age of the OMIT cohort was 67.4±13.2 years with an average T2D duration of 12.3±8.3 years (**Table 1**). The mean HbA_{1c} for the whole cohort through the study period was 7.6±1.5% (59.4±16.3 mmol/mol), BMI was 30.2±5.9 kg/m^2 and blood pressure 135±16.1/78±9.8 mmHg. The prevalence of retinopathy, coronary heart disease and stroke was 10.1%, 21% and 6.7%, respectively. Missing data varied greatly depending on the variable, with only 2.5% of the

cohort missing HbA_{1c} measures, while up to 52.6% were missing urinary albumin creatinine ratio (ACR).

Table 1. Total population characteristics and by separate data source (first wave linkages)

	Total (n = 57527) 2006 - 2019		ROSA4 (n = 10242) 2012 - 2014		NDR-A Primary Care (n = 42239) 2009 - 2019		NDR-A Hospital (n = 13876) 2006 - 2019	
	n (% missing)	mean (SD) or count (%)	n (% missing)	mean (SD) or count (%)	n (% missing)	mean (SD) or count (%)	n (% missing)	mean (SD) or count (%)
Sex- male	57527 (0.0%)	33367 (58.0%)	10242 (0.0%)	5626 (54.9%)	42239 (0.0%)	24211 (57.3%)	13876 (0.0%)	8620 (62.1%)
Age- years	57527 (0.0%)	67.4 (13.2)	10242 (0.0%)	69.8 (13.1)	42239 (0.0%)	68.3 (12.6)	13876 (0.0%)	63.0 (13.6)
Smoking- ever	52767 (8.3%)	28850 (54.7%)	7541 (26.4%)	3215 (42.6%)	37261 (11.8%)	20888 (56.1%)	8233 (40.7%)	5015 (60.9%)
Age at diagnosis- years	55303 (3.9%)	54.9 (12.9)	9769 (4.6%)	56.0 (12.9)	40755 (3.5%)	56.4 (12.4)	13492 (2.8%)	48.3 (12.6)
Diabetes duration- years	55303 (3.9%)	12.3 (8.3)	9769 (4.6%)	13.6 (7.0)	40755 (3.5%)	11.8 (8.0)	13492 (2.8%)	14.5 (9.1)
HbA_{1c}- %	56092 (2.5%)	7.6 (1.5)	9931 (3.0%)	7.2 (1.3)	40689 (3.7%)	7.2 (1.2)	13775 (0.7%)	8.1 (1.7)
HbA_{1c}- mmol/mol		59.4 (16.3)		54.8 (14.1)		55.4 (13.2)		65.4 (18.1)
BMI- kg/m^2	49983 (13.1%)	30.2 (5.9)	4662 (54.5%)	30.2 (6.0)	38255 (9.4%)	29.8 (5.9)	12635 (8.9%)	31.6 (6.2)
Systolic blood pressure- mmHg	52801 (8.2%)	135.0 (16.1)	8965 (12.5%)	135.0 (16.8)	38922 (7.9%)	135.0 (15.7)	11877 (14.4%)	135.0 (17.4)
Diastolic blood pressure- mmHg	52800 (8.2%)	78.0 (9.8)	8965 (12.5%)	78.0 (9.5)	38922 (7.9%)	77.6 (9.5)	11877 (14.4%)	78.1 (10.6)
Total cholesterol- mmol/L	50587 (12.1%)	4.6 (1.3)	9055 (11.6%)	4.7 (1.2)	35161 (16.8%)	4.5 (1.2)	13458 (3.0%)	4.7 (1.4)
HDL cholesterol- mmol/L	49114 (14.6%)	1.2 (0.4)	8776 (14.3%)	1.2 (0.4)	33773 (20.0%)	1.2 (0.4)	13414 (3.3%)	1.1 (0.3)
LDL cholesterol- mmol/L	49208 (14.5%)	2.7 (1.0)	8586 (16.1%)	2.8 (1.0)	34160 (19.1%)	2.7 (1.0)	13228 (4.7%)	2.7 (1.0)
Triglycerides- mmol/L	41715 (27.5%)	2.4 (2.8)	7335 (28.4%)	2.0 (1.8)	26594 (37.0%)	2.0 (1.7)	13240 (4.6%)	2.7 (3.5)
ACR*- mg/g	27253 (52.6%)	18.4 (75.4)	-	-	17301 (59.0%)	6.7 (33.0)	11033 (20.5%)	26.7 (93.7)
eGFR- ml/min/1.73^2	53142 (7.6%)	78.7 (30.8)	9701 (5.3%)	82.0 (24.3)	37488 (11.2%)	82.7 (25.1)	13665 (15.2%)	77.0 (32.9)
Retinopathy- yes	50638 (12.0%)	5138 (10.1%)	7570 (26.1%)	798 (10.5%)	38826 (8.1%)	2839 (7.3%)	11211 (19.2%)	2300 (20.5%)
Coronary heart disease- yes	54152 (5.9%)	11396 (21.0%)	10232 (0.1%)	2260 (22.1%)	40801 (3.4%)	8483 (20.8%)	11186 (19.4%)	2324 (20.8%)
Stroke- yes	53913 (6.3%)	3551 (6.7%)	10233 (0.1%)	758 (7.4%)	40601 (3.9%)	2563 (6.3%)	11124 (19.8%)	679 (6.1%)
Amputation- yes	52332 (9.0%)	489 (0.9%)	10233 (0.1%)	76 (0.7%)	38838 (8.1%)	214 (0.6%)	10207 (26.4%)	268 (2.6%)
Self-management course- completed	47467 (8.3%)	10326 (21.8%)	2257 (78%)	639 (28.3%)	39028 (7.6%)	9028 (23.1%)	11416 (17.7%)	2760 (24.2%)

*ACR values in this table are only derived from the NDR-A (primary care and hospital) records, excluding ROSA4, due to differences in reporting;
ACR = albumin creatinine ratio, BMI = body mass index, eGFR = estimated glomerular filtration rate, HDL = high density lipoprotein, LDL = low density lipoprotein, NDR-A = Norwegian Diabetes Register-Adult, ROSA4 = Rogaland Hordaland Oslo Salten Akershus 4 Study, SD = standard deviation
NB: Patients may be registered in multiple sources. The total, however, indicates the overall mean for identified 57,527 individual patients. Presented means give the time-weighted average for the entire follow-up period.

Table 1 shows only the main diabetes-related variables by source, and how data from different sources can be mutually supplementary to reduce the impact of missing data obtained from a single source. For example, 14.4% were missing blood pressure measurements from NDR-A hospital records, but due to the higher coverage by the NDR-A primary care records, only 8.2% of the whole cohort have missing blood pressure readings. Even though urinary ACR currently has a high amount of missing data, we will have the advantage of a large sample size in addition to a broad range of other co-variables (including estimates of glomerular filtration rate (eGFR) (calculated by use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations using serum creatinine measures[18])) which will allow imputation for missing ACR values.

The ROSA4 study, a seminal part of OMIT, has already published many studies related to T2D care in Norway, including findings that non-Western ethnic minorities are diagnosed with T2D at an earlier age than Westerners and are less likely to achieve target HbA_{1c} measures[19]. An early study demonstrated modest improvements in diabetes related risk markers from 2005 to 2014 in general practice, including HbA_{1c}, blood pressure and lipids, but revealed suboptimal screening for microvascular complications, such as nephopathy[15]. Another ROSA4 study indicated that point-of-care HbA_{1c} testing in general practice was linked to better glycaemic regulation in

patients with T2D[20]. Finally, ROSA4 has reported that GP adherence to recommended standard follow-up procedures in T2D was related to both clinic structure and workload[21].

Now that we have expanded the ROSA4 study, we are optimistic the OMIT cohort can further drive the work to enhance our knowledge about how we treat and care for patients with T2D in Norway. This work will position us to put forward concrete and tangible evidence-based recommendations on how diabetes care may be improved, with a special attention to high-risk patients.

Strengths and limitations

Strengths

The OMIT cohort is the first dedicated T2D cohort in Norway constructed from high-quality national registry data that includes patients from all counties, with increasing representativeness over time. Further, OMIT provides separate data from both outpatient clinics and general practices which enables studies of potential differences between these two patient populations. OMIT will support detailed analyses that will generate both nationally generalizable as well as internationally relevant findings. This surpasses the ability of studies such as HUNT and Tromsø Study, both of which are regionally restricted, rely partially on self-reported diabetes diagnoses

and have a lower sample size of patients with T2D[21]. Most OMIT data are longitudinal, which allows us to assess exposures at a time point prior to the defined outcomes. Also, OMIT will provide a basis for studying causes and effects of multi-morbidity rather than only traditional risk factors (e.g. hypertension, hyperglycaemia, hyperlipidaemia etc.). We currently have an extensive dataset that provides a full description of clinical features, socio-demographics, economy and ethnicity, drug prescriptions and drug retrievals, delivered care and treatment processes, and organizational factors including collaborations between primary and specialist care. This provides a strong basis for assessing possible relations between defined exposures and outcomes and to correct for a multitude of confounders. In order to explore potential causal factors, we will draw Directed Acyclic Graphs (DAGs) prior to analyses to identify true confounders to be adjusted for, in line with statistical methods developed to support causal inference in observational data.

Limitations

In this first wave of linkages, a substantial proportion of patients in the cohort are included from hospital outpatient clinics, which are likely to differ from patients cared for only in general practice, a condition reflected by a mean HbA_{1c} for the whole cohort as high as 7.6% (59.4±16.3 mmol/mol). Thus, sampling bias may be present and may require post-hoc corrections such as

stratification or inverse probability weighting. Further, there is risk that GPs willing to participate early on may have provided a higher level of care. This may also introduce bias, which could lower the external validity of primary care NDR-A data, particularly in the earlier years. Therefore, we plan to assess the overall representativeness of the NDR-A primary care data by use of the ROSA4-population, which is considered more representative for Norwegian general practice. Some variables have high levels of missing data, and follow-up time-periods vary between data sources and within patients. Thus, it may also be relevant to perform analysis of potential selection bias due to self-selection and missing data.

Data Availability Statement

All OMIT data are stored and analysed on the platform for safe storage of sensitive data (TSD) at the University of Oslo until 2035. In support of collaborative research projects, access can be granted after approval by the OMIT-study group, the Regional Committee for Medical and Health Research Ethics and the data owner at the University of Oslo. Project requests can be directed to Esben Selmer Buhl at the Department of General Practice, Institute of Health and Society, University of Oslo (email: e.s.buhl@medisin.uio.no)

Further details

Funding

The first phase of linkages was funded by the University of Oslo. Currently, senior researchers and one postdoctoral position (Western Norway University of Applied Sciences (HVL), Norway) are funded by their home institutions (for senior researchers: see author affiliation list). The cohort is also funded by The Norwegian Diabetes Association (Diabetesforbundet) and the Norwegian Research Fund for General Practice (Allmennmedisinsk forskningsfond), with the latter also funding one PhD-student (University of Oslo (UiO), Norway).

Ethics and ethics approval

The project has obtained ethical approval from Regional Committees for Medical Research Ethics - South East Norway (REC South East (Ref# 74012)) and is approved by the Data Protection Official/Officer at UiO. Data linkage began in mid-2020 for the years 2006-2019. After the final linkages of data from all registers, all researchers are not in any way be able to identify individual patients. We have reduced the number of categories for variables (data minimization) to secure a sufficient number in each cell so that patients cannot be retrospectively identified. Individual researchers will only have access to variables relevant for their research questions, and only after granted approval from REC South East.

Patient and Public Involvement

The OMIT-study has received a letter of endorsement from the Norwegian Diabetes Association in addition to financial support, and key senior researchers from the OMIT-study group, including Prof. Emeritus Anne Karen Jenum, over the years with the ROSA4-study have had a long-standing close collaboration with Norwegian Diabetes Association, which we aspire to continue with the OMIT-initiative.

To secure that the OMIT project will result in tangible and quantifiable improvements in the clinical care of high-risk patients with T2D, in alignment with patient preferences and identified unmet needs, we have the identified the following key strategic objectives and the related target stakeholder and tactics:

Strategic objective: **Strengthen GP diabetes education**.

- *Target stakeholder*: Norwegian Medical Association (Den Norske Legeforening (DNLF)) and Association of General Practitioners (*Allmennlegeforeningen*) – later on other Nordic Medical Associations may also be relevant.
- *Tactics*: Ensure a dedicated class with focus on high-risk patients is incorporated into the annual pre- and post-gradual national courses in diabetes.

Strategic objective: **Improve clinical guidelines for key high-risk patients.**

- *Target stakeholder*: Norwegian guideline author group.
- *Tactics*: Translate key research findings into concrete suggestions on how to individualize guidelines for high-risk patients and on how different drug regimens may help solve key clinical issues such as non-adherence, therapeutic inertia and disease control variability in high-risk patients.

Strategic objective: **Secure high-risk patients access to innovation (e.g. reimbursement).**

- *Target stakeholder:* The Norwegian Medicines Agency (Legemiddelverket (LMV)) and the Norwegian Directorate of Health (Helsedirektoratet).
- *Tactics*: Identify and share patient subgroups with most attractive cost-benefit-ratio.

Strategic objective: **Enhance patient competences and empowerment.**

- *Target stakeholder:* Norwegian Diabetes Association (Diabetes Forbundet).
- *Tactics:* Norwegian Diabetes Association has written a letter of endorsement and granted financial resources to support the OMIT-initiative. Going forward, in close dialogue with the Norwegian Diabetes Association, the OMIT-study group will ensure key research findings and key takeaways with relevance for patients will be communicated to patients, using both the webpage and the membership magazine of Norwegian Diabetes Association.

Strategic objective: **Improve political willingness to invest in high-risk patients.**

- *Target stakeholders:* Public media, Ministry of Health and Care Services and other political key decision makers.
- *Tactics:* Disseminate data and key takeaways related to current unmet needs in diabetes care but also communicate key conclusions regarding the effectiveness and cost-effectiveness of various treatments and interventions to build public and political awareness of inequality in diabetes outcomes and use evidence to shift focus from short-term budget impact to impact in the long-term on compiled disease life-cycle costs.

Strategic objective: **Ensure generated hypotheses are tested in prospective interventional studies.**

- *Target stakeholders:* Diabetes researchers in Norway and abroad and researchers involved in Norwegian general practice research network.
- *Tactics:* Ensure scientific data are presented at national and international scientific conferences and published in high-impact peer reviewed journals. In addition, identify hypotheses relevant to test in future prospective and interventional studies.

With this strategic approach, we aspire that the OMIT-project will help increase public awareness about unmet needs in current care, support patient empowerment by strengthening

patient organization competences, influence policy makers to perform relevant and cost-effective investments, improve national guidelines and facilitate that the right patients get access to right treatments at the right time.

Competing interests

All authors have filled out and signed a “Disclosure of potential conflicts of interests”-form which can be reproduced upon request. E.S. Buhl is a previous employee of Novo Nordisk (2011-16) and has offered medical consulting and lectures to Novo Nordisk, Sanofi Aventis and MundiPharma. J.G. Cooper has received lecturing fees from Novo Nordisk, Sanofi Aventis, Eli Lilly, AstraZeneca, GSK. All other authors declare no conflicts of interests.

Author contributions

Together Dr. E.S. Buhl and Prof. Emeritus A.K. Jenum have initiated and driven the work related to drafting the overall OMIT research protocol, to applying for local ethics committee approval and to the process of performing the register linkages. Dr. E.S. Buhl is the primary investigator (P.I.) on the OMIT-cohort study and Prof. M. M. Iversen has recently succeeded Prof. Emeritus Dr. A.K. Jenum in the role as Co-P.I.

Dr. K. Nøkleby, Dr. T. J. Berg, Prof. T. Iversen, Prof. T Hagen, Dr. J. Cooper, Prof. S. Sandberg and DrMsc. K. F. Løvaas have also provided substantial inputs to the overall OMIT-research protocol. After local ethics committee approval of the study-protocol, Dr. K. R. Richardsen, Prof. R. M. Nilsen and Prof. M. M. Iversen have joined the OMIT-study group, and co-P.I. Prof. M. M. Iversen has contributed substantially with the refinement of some of the research questions related to the protocol as well as to the strategic planning of the overall project. The first three Ph.D/Post.Doc.-research projects, out of six planned for the time being, originating from the protocol are in the process of being executed as a 1) PhD.-project focusing on complications in YOD patients (Dr. K. Tibballs based at University of Oslo (UiO) with Dr. E.S. Buhl as supervisor), 2) as a Post.Doc.-project assessing quality of care in elderly with T2D (Dr. R. B. Strandberg based at Western Norway University of Applied Sciences (HVL) with Prof. M.M. Iversen as supervisor) and 3) a Post.Doc.-project focusing on real-life drug effectiveness in YOD and elderly patients with T2D (candidate to be determined).

Dr. R. B. Forster has worked with the initial analyses and quality check of the data files and has first authored this cohort paper. All other researchers mentioned above each have contributed significantly with the writing and review of this manuscript with last author and P.I. Dr. E. S. Buhl taking the role as corresponding author.

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Figure legends

Figure 1.

Overview of OMIT cohort construction, covered time-periods and overall data categories and co-variables.

Figure 2.

Number of OMIT cohort patients by source and year (first wave linkages).

The bars shown above only indicate the number of OMIT-patients reported to the NDR-A registry. Although reporting to the NDR-A registry did not start until 2008, please note that the current cohort still includes some outpatient hospital data for the years 2006-2007. The green and transparent bars, placed in a front position, reflect the number of patients by year reported to NDR-A by hospital clinics, whereas violet bars, placed behind the green transparent bars, give the number of patients reported by year to the NDR-A by GPs. For the years 2012-14, please note that the ROSA4-data base contributed with additional 4,573 GP patients to the cohort which, however, are not accounted for in the shown violet bars.

Figure 3.

Venn diagram of overlap for total number of registered patients in OMIT cohort, with the first wave linkages, from the three different sources.

NB: When accounting for those overlaps, please note that the first wave cohort has enrolled 57,527 individual patients with type 2 diabetes.

Figure 4.

Number of registered OMIT patients by year by county, standardised to total county population.

County legend, e.g. ISO-codes: 1. Østfold; 2 Akershus; 3 Oslo; 4 Hedmark; 5 Oppland; 6 Buskerud; 7 Vestfold; 8 Telemark; 9 Aust-Agder; 10 Vest-Agder; 11 Rogaland; 12 Hordaland; 14 Sogn og Fjordane; 15 Møre og Romsdal; 16 Sør-Trøndelag*; 17 Nord-Trøndelag*; 18 Troms; 20 Finnmark.

* In 2019 Nør- and Sør-Trøndeag were combined in to a single county, Tøndelag, ISO-code 50.

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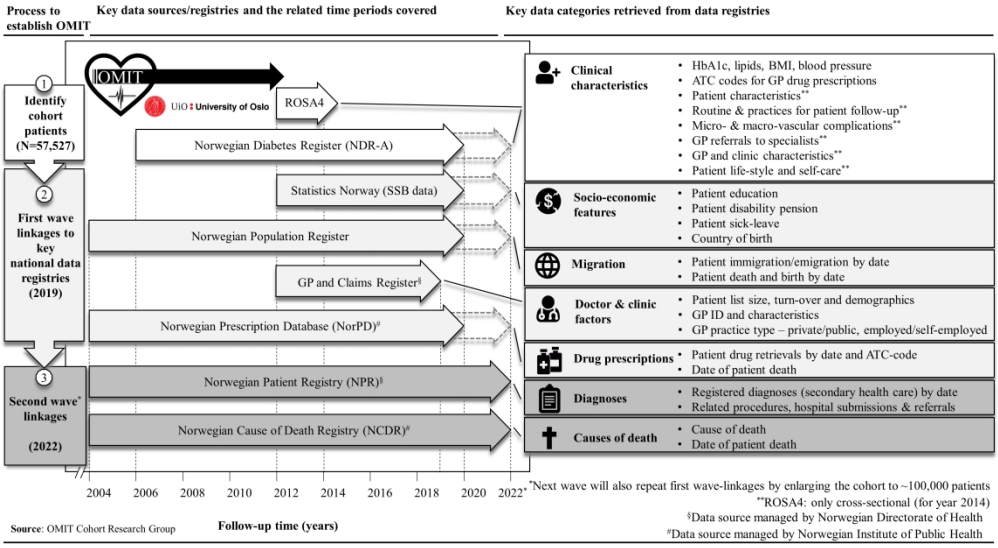

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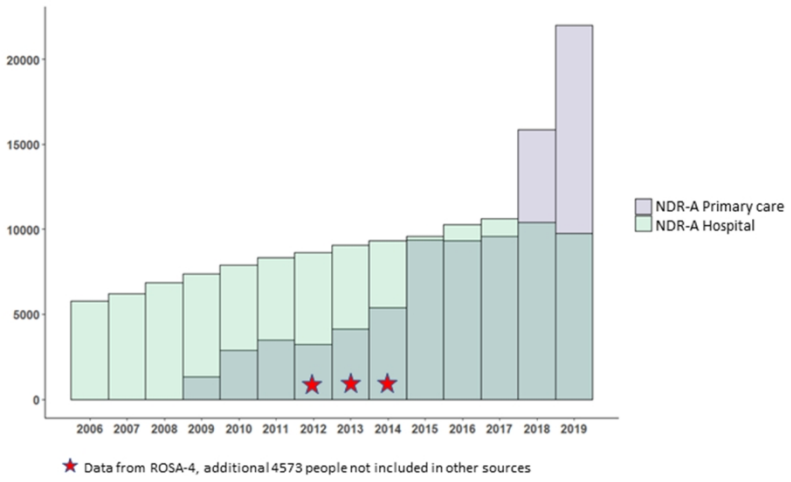

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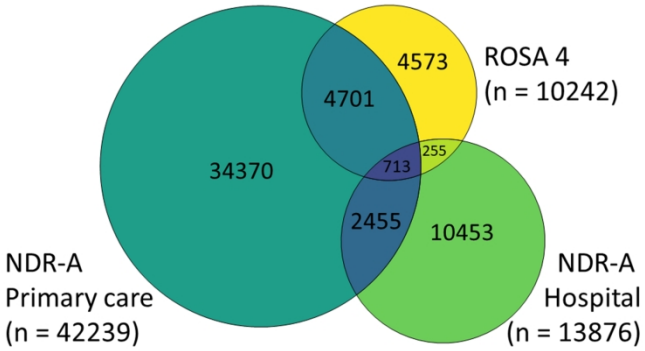

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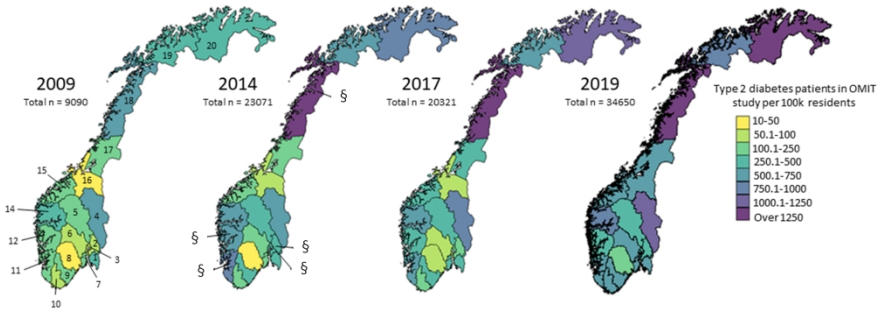

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Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) – a national registry-based observational cohort with focus on care and treatment of key high-risk groups in Norway

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V5 19/12/2021

Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) – a national registry-based observational cohort with focus on care and treatment of key high-risk groups in Norway

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Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)

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V5 19/12/2021

Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)

Abstract (word count: 291 (max. 300))

Purpose: The "Outcomes & Multi-morbidity in Type 2 Diabetes" (OMIT) is an observational registry-based cohort of Norwegian patients with type 2 diabetes (T2D) established to study high-risk groups often omitted from randomized clinical trials.

Participants: The OMIT cohort includes 57,572 patients with T2D identified via linkage of Norwegian Diabetes Register for Adults (NDR-A) and the Rogaland-Oslo-Salten-Akershus-Hordaland (ROSA4) study, both offering data on clinical patient characteristics and drug prescriptions. Subsequently these data are further linked to the Norwegian Prescription Database for dispensed medications, the Norwegian Population Register for data on death and migration, Statistics Norway for data on socio-economic factors and ethnicity and the Norwegian Directorate of Health for data on the general practices and clinical procedures involved in the care of cohort patients. OMIT offers large samples for key high-risk patient groups: 1) young-onset diabetes (T2D at age <40 years) (n = 6,510), 2) elderly (age >75 years) (n = 15,540), 3) non-Western ethnic minorities (n ~9,000) and 4) low socioeconomic status (n ~20,500).

Findings to date: On average, patient age and diabetes duration is 67.4 ±13.2 and 12.3 ±8.3 years, respectively, and mean HbA_{1c} for the whole cohort through the study period is 7.6±1.5%

(59.4±16.3 mmol/mol), mean BMI and blood pressure is 30.2±5.9 kg/m^2 and 135±16.1/78±9.8 mmHg, respectively. Prevalence of retinopathy, coronary heart disease and stroke is 10.1%, 21% and 6.7%, respectively.

Future plans: The OMIT cohort features 5,784 subjects with T2D in 2006, a number that has grown to 57,527 in 2019 and is expected to grow further via repeated linkages performed every third to fifth year. At the next wave of data collection, additional linkages to Norwegian Patient Registry and Norwegian Cause of Death Registry for data on registered diagnoses and causes of death, respectively, will be performed.

Strengths and limitations of this cohort

- The Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) cohort offers large sample size (between 2006 to 2019 including 57,527 patients) and over time growing regional representativeness.
- OMIT is produced from multiple linkages of high-quality Norwegian data-registries, with Norwegian Diabetes Register for Adults (NDR-A) as the primary source to identify patients, covering a wide range of key data-categories.

- OMIT is expected to grow further and to offer even more exhaustive data via repeated linkages performed every third to fifth year.

- OMIT may not be fully representative for Norwegian general practice, especially in the earlier years, as many of the patients then were included from hospital outpatient clinics and are likely to differ from patients cared for only in general practice.

- There may be a risk of self-selection bias, especially for the earlier years, as those GPs willing to report data early on may have provided a higher level of care.

Introduction

Background

The prevalence of Type 2 diabetes (T2D) is increasing worldwide, and so is the burden of related vascular complications and death[1]. Diabetes is a major cause of cardiovascular disease, blindness[2], chronic kidney disease[3], diabetic foot ulcers[4] and limb amputations[5]. Beyond the immense reduction in quality of life, these complications lead to reduced labour market participation and inflict a considerable burden on the global economy[6].

Although timely and efficacious interventions can improve outcomes and reduce the economic burden[7], the evidence for current drug regimens is often limited in patients with greater needs as they are often omitted from clinical trials. Clinical guidelines from the European Association for the Study of Diabetes (EASD)[8], the American Diabetes Association[9] and Norwegian Directorate of Health[10] provide guidance on how to manage diabetes treatments and disease control targets based on an individualized approach. However, a key weakness is the guidelines are based on results from trials where only 3.5–35.7% of patients in daily clinical practice would have been eligible to participate[11]. Therefore, the results from these trials may not be generalizable for the majority of patients, especially vulnerable groups such as 1) those with young onset diabetes (T2D prior to age 40), 2) elderly above 75 years, 3) ethnic minorities, and 4) patients with low

socio-economic status. Moreover, guidelines provide only a vague guidance as to how diabetes care should be customized and organized in a general practice setting and fail to deliver clear recommendations on how to address a broad range of key barriers to good disease control for vulnerable groups[12]. Consequently, we need more evidence to better understand the current unmet needs and evidence documenting the effectiveness, cost-effectiveness and safety of various treatments and clinical procedures in relation to how they may impact both disease control and harder disease outcomes in high-risk patients. As high-risk patients have proven difficult to include in prospective interventional trials, instead we see a great opportunity to employ non-interventional, observational data already present in various high-quality national registries.

The “Outcomes & Multi-morbidity in Type 2 Diabetes” (OMIT) cohort, which is based on multiple linkages between various Norwegian population-based registries, was established to support non-interventional observational studies of high-risk patients with T2D treated in general practice, in outpatient hospital clinics, or by shared care. The first wave of the OMIT cohort focus primarily on the following key high-risk groups: (1) young onset diabetes (YOD - T2D prior to age 40), (2) elderly patients (>75 years of age), (3) non-western ethnic minorities (i.e. non-western immigrants excluding Eastern European immigrants), and (4) low socio-economic status (SES)

patients. Low SES defined here as having only primary level education. The OMIT-cohort will also have data to support more refined SES-definitions accounting for personal and household income, as well as employment status (for those in working age).

OMIT research questions

Currently, we have three broad research questions:

(1) How does multi-morbidity interact with diabetes development and care, and how is it related to intermediate (e.g HbA_{1c}, LDL and/or blood pressure) and harder disease outcomes (e.g. diabetes-specific complications and/or death)?

(2) How do newer anti-diabetic drugs perform in terms of real-life effectiveness (e.g. as opposed to drug efficacy, which can be measured only in randomized clinical trials), cost-effectiveness, safety and adherence in high-risk groups?

(3) What are the causes and effects of diabetes control variability on intermediate and harder disease outcomes and how is the organization of diabetes care related to these outcomes?

To answer the overall research questions, we have planned several individual studies to investigate the following outcomes in key high-risk patient groups (ranked in descending order according to number of planned studies) (please see Figure 1):

- Primary outcomes: (1) Multi-morbidity, (2) diabetes-specific complications, (3) mortality/survival, (4) variability in disease control (e.g. variability in relation to intermediate disease outcomes), (5) drug effectiveness and cost-effectiveness, (6) drug adherence and (7) YOD.
- Secondary outcomes: (1) Anatomical Therapeutic Chemical (ATC) classification code based co-morbidity, (2) mortality, (3) diabetes-specific complications, (4) drug adherence, (5) drug treatment cascade, (6) drug effectiveness and cost-effectiveness, (7) polypharmacy and risk of potentially adverse drug interactions, (8) variability in disease control (e.g. variability in relation to intermediate disease outcomes), (9) YOD and (10) disability pension/sick leave.

Cohort description

Data sources and categories

NDR-A and ROSA4: The NDR-A and ROSA4 databases include a wide array of demographic and clinical data. These data include year of birth, sex and regional location, diabetes variables including year of diagnosis and HbA_{1c} measures, as well as blood pressure and lipid measurements and prescribed medications. We have also collected important vascular outcomes such as retinopathy, cardiovascular disease, nephropathy and markers of neuropathy that include evidence of foot ulcers, monofilament foot examinations and pulse testing. **Table 1** provides an overview of some of the important clinical variables collected from NDR-A and ROSA4.

Statistics Norway (SSB): Data gathered from Statistics Norway mainly cover socio-economic factors, including education, disability income, sick-leave and country of birth.

Norwegian Population Register (NPR): This register will provide detailed information on migration of the patients within the study, including dates for immigration and/or emigration and death.

Norwegian Prescription Database (NorPD): NorPD data represent all dispensed prescriptions by date and ATC-codes for each participant. The OMIT cohort also obtains date of death from NorPD.

Further, based on ATC codes we will construct an ATC-code based multi-morbidity score[13], which will be validated based on its ability to predict 1- and 5-year mortality. The score will then serve as an individual measure applicable as either an exposure or an outcome in subsequent research studies.

Norwegian Directorate of Health: The Norwegian Directorate of Health manages several national registers, including the medical claims register (KUHR) and the Health Personnel Register (HPR), from which we will receive data on GPs and features of their clinical practices. This includes patient list size, waiting list size, patient turnover data and demographics. GP characteristics include specialist status and whether the GP is salaried or self-employed, as well as an overview of the procedure-related payments and diagnoses recorded by the GP, enabling analyses of health economic outcomes.

Patient enrolment and sample size

The eligibility criteria for the OMIT cohort are all T2D patients over 18 years. All patients are identified from the Norwegian Diabetes Register for Adults (NDR-A) or the Rogaland-Oslo-Salten-Akershus-Hordaland (ROSA 4) study, covering the time-period from 2006 to 2019. Subsequently, these data sources are linked to the Norwegian Prescription Database for dispensed medications, the Norwegian Population Register for data on death and migration,

Statistics Norway for data on socio-economic factors and ethnicity and the Norwegian Directorate of Health for data on the general practices and clinical procedures involved in the care of cohort patients.

Figure 2 shows the different cohort-data sources, the time-periods covered with the first and second wave register linkages and the different data categories made available for the included cohort patients. For more details, please see chapter “Data sources and categories” below. First wave linkages involves data until December 31st 2019 whereas second wave linkages will extend covered time period until December 31st 2022 and supplement the cohort with additional data from the Norwegian Patient Registry and Norwegian Cause of Death Registry.

The NDR-A was established in 2005 with the aim of improving the quality of treatment of people with diabetes in Norway[14]. The registry has included outpatient hospital data since 2006, although reporting did not start until 2008. Primary care data has been included since 2009. Since then, the number of included patients in NDR-A has grown steadily. However, mainly due to requirements of written informed consent, enrolment was low in the early years, especially for people with T2D. In response, the ROSA 4 study was created to secure access to representative data on patients with diabetes from diverse clinical settings. ROSA4 is a population-based cross-

sectional survey conducted in 2015 (but based on data from the time period 2012-2014) that included 10,248 people with T2D identified by 282 general practitioners (GPs) [15].

As an extension of the past initiatives, the "Outcomes & Multi-morbidity in Type 2 Diabetes" (OMIT) project has now combined data from the NDR-A and ROSA4. OMIT will carry forward previous research efforts focusing on the quality of care for people with T2D in Norway, although this time with a dedicated focus on high-risk groups often omitted from randomized clinical trials (hence the acronym OMIT).

Figure 3 shows the number of OMIT cohort patients by source and year, as well as patient enrolment over time organized by hospital and primary care sources. **Figure 3** also shows that ROSA4 contributed data in the time-period 2012-2014, although some ROSA4 patients may also have been in the NDR-A prior to and after these years. The ROSA4 study comprises longitudinal laboratory and drug prescription data from 2012-2014 and cross-sectional data on other patient characteristics from 2014. When considering the overlap with the NDR-A, ROSA4 delivered an additional 4,573 patients to the OMIT cohort. Going forward, we expect the cohort to grow further as a more GPs report to the register. Recent changes in national regulations have made it possible for national health registers to apply for inclusion of patients without informed consent if patients have not proactively put forward a request to be excluded[16]. In addition, The

Norwegian Health Economics Administration (HELFO) has recently introduced a payments to GPs who submit data to the NDR-A. This is likely to accelerate GP reporting further. Consequently, the OMIT cohort is expected to grow to ~100,000 patients with T2D in 2022 (second wave linkages).

Between 2006 and 2019, a total of 57,527 individuals have been included in OMIT. Hereof 10,242 patients from the ROSA4 study, 42,239 from the NDR-A primary care database and 13,876 from the NDR-A hospital database. There is substantial overlap between the databases (**Figure 4**). For the high-risk groups, the current cohort includes data for about 6,500 YOD patients, 15,500 elderly (>75 years), about 9,000 non-western ethnic minority patients, e.g. predominantly South and East Asian or African ethnical background, and 20,500 patients with primary education only.

Figure 5 illustrates development in the national coverage of the cohort via a series of maps, identifying the different counties of Norway. The fill colour indicates the county's total number of registered patients in OMIT, standardized to county population. In 2009, several counties had low coverage, such as the counties Sør-Trøndelag and Telemark, but this has improved over time to all counties having over 100 T2D patients per 100,000 residents included in the OMIT cohort in 2019, and several counties have over 1000 patients per 100,000. Although roughly

one-third of GPs reported patients to the NDR–A in 2019, the OMIT-cohort at present only includes about 20% of the T2D population in Norway[17]. However, all counties are represented, and thus it offers good reliability when studying populations that may differ regionally.

Patient follow-up

The first wave linkages included all data in NDR-A and ROSA4 up until the end of 2019. Patients are generally followed up at least once per year as one annual diabetes control is recommended as the minimum in general practice and GPs now receive a payment per patient for performing annual follow-up and reporting data to the NDR-A. In the current cohort, the median follow-up time between the first and final HbA_{1c} measures is 2 years, with an interquartile range (IQR) of 0 to 7 years and maximum of 14 years. The median number of visits is 6 (IQR 1 to 139). Despite having access to data from 2006 to 2009, the median follow-up reflects a large increase in first recordings in NDR-A in 2018 and 2019. To see clinical characteristics of current study participants, please see Table 1 (for more details, please see Chapter “Findings to date”).

Future patient enrolment and sample sizes

Going forward, we expect the NDR-A, e.g. the primary source for including patients into OMIT, to include recurring annual data for a growing proportion of the cohort-patients as more GPs are likely to report. Further, the number of recorded measurements per year, especially concerning

HbA_{1c}, blood pressure and drug prescriptions, are likely to increase as GPs tend to follow-up their patients more frequently as compared to the outpatient hospital clinics. As already stated, to increase the sample size of the cohort, we therefore plan to replicate the linkages with new waves of data every three to five years. Thus, we expect the NDR-A to grow, with 15 000 new patients, as observed during 2019, to about 30 000 new patients annually over the next five years. As a result, we expect the OMIT cohort to increase to approximately 100,000 and 150,000 patients in 2022 (second wave linkages) and 2025 (third wave linkages), respectively. In addition, already with the second wave, it is planned for the OMIT cohort to be further linked with the Norwegian Patient Registry and the Norwegian Cause of Death Registry. This will further strengthen the comprehensiveness of the cohort and prove solid ground for future studies focusing on mortality related outcomes.

Findings to date

In 2019, the average age of the OMIT cohort was 67.4±13.2 years with an average T2D duration of 12.3±8.3 years (**Table 1**). The mean HbA_{1c} for the whole cohort through the study period was 7.6±1.5% (59.4±16.3 mmol/mol), BMI was 30.2±5.9 kg/m^2 and blood pressure 135±16.1/78±9.8 mmHg. The prevalence of retinopathy, coronary heart disease and stroke was 10.1%, 21% and

6.7%, respectively. Missing data varied greatly depending on the variable, with only 2.5% of the cohort missing HbA_{1c} measures, while up to 52.6% were missing urinary albumin creatinine ratio (ACR).

Table 1. Total population characteristics and by separate data source (first wave linkages)

	Total (n = 57527) 2006 - 2019		ROSA4 (n = 10242) 2012 - 2014		NDR-A Primary Care (n = 42239) 2009 - 2019		NDR-A Hospital (n = 13876) 2006 - 2019	
	n (% missing)	mean (SD) or count (%)	n (% missing)	mean (SD) or count (%)	n (% missing)	mean (SD) or count (%)	n (% missing)	mean (SD) or count (%)
Sex- male	57527 (0.0%)	33367 (58.0%)	10242 (0.0%)	5626 (54.9%)	42239 (0.0%)	24211 (57.3%)	13876 (0.0%)	8620 (62.1%)
Age- years	57527 (0.0%)	67.4 (13.2)	10242 (0.0%)	69.8 (13.1)	42239 (0.0%)	68.3 (12.6)	13876 (0.0%)	63.0 (13.6)
Smoking- ever	52767 (8.3%)	28850 (54.7%)	7541 (26.4%)	3215 (42.6%)	37261 (11.8%)	20888 (56.1%)	8233 (40.7%)	5015 (60.9%)
Age at diagnosis- years	55303 (3.9%)	54.9 (12.9)	9769 (4.6%)	56.0 (12.9)	40755 (3.5%)	56.4 (12.4)	13492 (2.8%)	48.3 (12.6)
Diabetes duration- years	55303 (3.9%)	12.3 (8.3)	9769 (4.6%)	13.6 (7.0)	40755 (3.5%)	11.8 (8.0)	13492 (2.8%)	14.5 (9.1)
HbA_{1c}- %	56092 (2.5%)	7.6 (1.5)	9931 (3.0%)	7.2 (1.3)	40689 (3.7%)	7.2 (1.2)	13775 (0.7%)	8.1 (1.7)
HbA_{1c}- mmol/mol		59.4 (16.3)		54.8 (14.1)		55.4 (13.2)		65.4 (18.1)
BMI- kg/m^2	49983 (13.1%)	30.2 (5.9)	4662 (54.5%)	30.2 (6.0)	38255 (9.4%)	29.8 (5.9)	12635 (8.9%)	31.6 (6.2)
Systolic blood pressure- mmHg	52801 (8.2%)	135.0 (16.1)	8965 (12.5%)	135.0 (16.8)	38922 (7.9%)	135.0 (15.7)	11877 (14.4%)	135.0 (17.4)
Diastolic blood pressure- mmHg	52800 (8.2%)	78.0 (9.8)	8965 (12.5%)	78.0 (9.5)	38922 (7.9%)	77.6 (9.5)	11877 (14.4%)	78.1 (10.6)
Total cholesterol- mmol/L	50587 (12.1%)	4.6 (1.3)	9055 (11.6%)	4.7 (1.2)	35161 (16.8%)	4.5 (1.2)	13458 (3.0%)	4.7 (1.4)
HDL cholesterol- mmol/L	49114 (14.6%)	1.2 (0.4)	8776 (14.3%)	1.2 (0.4)	33773 (20.0%)	1.2 (0.4)	13414 (3.3%)	1.1 (0.3)
LDL cholesterol- mmol/L	49208 (14.5%)	2.7 (1.0)	8586 (16.1%)	2.8 (1.0)	34160 (19.1%)	2.7 (1.0)	13228 (4.7%)	2.7 (1.0)
Triglycerides- mmol/L	41715 (27.5%)	2.4 (2.8)	7335 (28.4%)	2.0 (1.8)	26594 (37.0%)	2.0 (1.7)	13240 (4.6%)	2.7 (3.5)
ACR*- mg/g	27253 (52.6%)	18.4 (75.4)	-	-	17301 (59.0%)	6.7 (33.0)	11033 (20.5%)	26.7 (93.7)
eGFR- ml/min/1.73^2	53142 (7.6%)	78.7 (30.8)	9701 (5.3%)	82.0 (24.3)	37488 (11.2%)	82.7 (25.1)	13665 (15.2%)	77.0 (32.9)
Retinopathy- yes	50638 (12.0%)	5138 (10.1%)	7570 (26.1%)	798 (10.5%)	38826 (8.1%)	2839 (7.3%)	11211 (19.2%)	2300 (20.5%)
Coronary heart disease- yes	54152 (5.9%)	11396 (21.0%)	10232 (0.1%)	2260 (22.1%)	40801 (3.4%)	8483 (20.8%)	11186 (19.4%)	2324 (20.8%)
Stroke- yes	53913 (6.3%)	3551 (6.7%)	10233 (0.1%)	758 (7.4%)	40601 (3.9%)	2563 (6.3%)	11124 (19.8%)	679 (6.1%)
Amputation- yes	52332 (9.0%)	489 (0.9%)	10233 (0.1%)	76 (0.7%)	38838 (8.1%)	214 (0.6%)	10207 (26.4%)	268 (2.6%)
Self-management course- completed	47467 (8.3%)	10326 (21.8%)	2257 (78%)	639 (28.3%)	39028 (7.6%)	9028 (23.1%)	11416 (17.7%)	2760 (24.2%)

*ACR values in this table are only derived from the NDR-A (primary care and hospital) records, excluding ROSA4, due to differences in reporting;
ACR = albumin creatinine ratio, BMI = body mass index, eGFR = estimated glomerular filtration rate, HDL = high density lipoprotein, LDL = low density lipoprotein, NDR-A = Norwegian Diabetes Register-Adult, ROSA4 = Rogaland Hordaland Oslo Salten Akershus 4 Study, SD = standard deviation
The reported prevalent complications, incl. self-management course, represent the status for each participant at the last follow-up.

NB: Patients may be registered in multiple sources and with multiple measurements. The total, however, indicates the overall mean for identified 57,527 individual patients. Presented means are based on the time-weighted average calculated for each patient for the entire follow-up period.

Table 1 shows only the main diabetes-related variables by source, and how data from different sources can be mutually supplementary to reduce the impact of missing data obtained from a single source. For example, 14.4% were missing blood pressure measurements from NDR-A hospital records, but due to the higher coverage by the NDR-A primary care records, only 8.2% of the whole cohort have missing blood pressure readings. Even though urinary ACR currently has a high amount of missing data, we will have the advantage of a large sample size in addition to a broad range of other co-variables (including estimates of glomerular filtration rate (eGFR) (calculated by use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations using serum creatinine measures[18])) which will allow imputation for missing ACR values.

The ROSA4 study, a seminal part of OMIT, has already published many studies related to T2D care in Norway, including findings that non-Western ethnic minorities are diagnosed with T2D at an earlier age than Westerners and are less likely to achieve target HbA_{1c} measures[19]. An early study demonstrated modest improvements in diabetes related risk markers from 2005 to 2014 in general practice, including HbA_{1c}, blood pressure and lipids, but revealed suboptimal screening for microvascular complications, such as nephopathy[15]. Another ROSA4 study indicated that

point-of-care HbA_{1c} testing in general practice was linked to better glycaemic regulation in patients with T2D[20]. Finally, ROSA4 has reported that GP adherence to recommended standard follow-up procedures in T2D was related to both clinic structure and workload[21].

Now that we have expanded the ROSA4 study, we are optimistic the OMIT cohort can further drive the work to enhance our knowledge about how we treat and care for patients with T2D in Norway. This work will position us to put forward concrete and tangible evidence-based recommendations on how diabetes care may be improved, with a special attention to high-risk patients.

Strengths and limitations

Strengths

The OMIT cohort is the first dedicated T2D cohort in Norway constructed from high-quality national registry data that includes patients from all counties, with increasing representativeness over time. Further, OMIT provides separate data from both outpatient clinics and general practices which enables studies of potential differences between these two patient populations. OMIT will support detailed analyses that will generate both nationally generalizable as well as internationally relevant findings. This surpasses the ability of studies such as HUNT and Tromsø

Study, both of which are regionally restricted, rely partially on self-reported diabetes diagnoses and have a lower sample size of patients with T2D[21]. Most OMIT data are longitudinal, which allows us to assess exposures at a time point prior to the defined outcomes. Also, OMIT will provide a basis for studying causes and effects of multi-morbidity rather than only traditional risk factors (e.g. hypertension, hyperglycaemia, hyperlipidaemia etc.). We currently have an extensive dataset that provides a full description of clinical features, socio-demographics, economy and ethnicity, drug prescriptions and drug retrievals, delivered care and treatment processes, and organizational factors including collaborations between primary and specialist care. This provides a strong basis for assessing possible relations between defined exposures and outcomes and to correct for a multitude of confounders. In order to explore potential causal factors, we will draw Directed Acyclic Graphs (DAGs) prior to analyses to identify true confounders to be adjusted for, in line with statistical methods developed to support causal inference in observational data.

Limitations

In this first wave of linkages, a substantial proportion of patients in the cohort are included from hospital outpatient clinics, which are likely to differ from patients cared for only in general practice, a condition reflected by a mean HbA_{1c} for the whole cohort as high as 7.6% (59.4±16.3

mmol/mol). Thus, sampling bias may be present and may require post-hoc corrections such as stratification or inverse probability weighting. Further, there is risk that GPs willing to participate early on may have provided a higher level of care. This may also introduce bias, which could lower the external validity of primary care NDR-A data, particularly in the earlier years. Therefore, we plan to assess the overall representativeness of the NDR-A primary care data by use of the ROSA4-population, which is considered more representative for Norwegian general practice. Some variables have high levels of missing data, and follow-up time-periods vary between data sources and within patients. Thus, it may also be relevant to perform analysis of potential selection bias due to self-selection and missing data.

Data Availability Statement

All OMIT data are stored and analysed on the platform for safe storage of sensitive data (TSD) at the University of Oslo until 2035. In support of collaborative research projects, access can be granted after approval by the OMIT-study group, the Regional Committee for Medical and Health Research Ethics and the data owner at the University of Oslo. Project requests can be directed to Esben Selmer Buhl at the Department of General Practice, Institute of Health and Society, University of Oslo (email: e.s.buhl@medisin.uio.no)

Further details

Funding

The first phase of linkages was funded by the University of Oslo. Currently, senior researchers and one postdoctoral position (Western Norway University of Applied Sciences (HVL), Norway) are funded by their home institutions (for senior researchers: see author affiliation list). The cohort is also funded by The Norwegian Diabetes Association (Diabetesforbundet) and the Norwegian Research Fund for General Practice (Allmennmedisinsk forskningsfond), with the latter also funding one PhD-student (University of Oslo (UiO), Norway).

Ethics and ethics approval

The project has obtained ethical approval from Regional Committees for Medical Research Ethics - South East Norway (REC South East (Ref# 74012)) and is approved by the Data Protection Official/Officer at UiO. Data linkage began in mid-2020 for the years 2006-2019. After the final linkages of data from all registers, all researchers are not in any way be able to identify individual patients. We have reduced the number of categories for variables (data minimization) to secure a sufficient number in each cell so that patients cannot be retrospectively identified. Individual researchers will only have access to variables relevant for their research questions, and only after granted approval from REC South East.

Patient and Public Involvement

The OMIT-study has received a letter of endorsement from the Norwegian Diabetes Association in addition to financial support, and key senior researchers from the OMIT-study group, including Prof. Emeritus Anne Karen Jenum, over the years with the ROSA4-study have had a long-standing close collaboration with Norwegian Diabetes Association, which we aspire to continue with the OMIT-initiative.

To secure that the OMIT project will result in tangible and quantifiable improvements in the clinical care of high-risk patients with T2D, in alignment with patient preferences and identified unmet needs, we have the identified the following key strategic objectives and the related target stakeholder and tactics:

Strategic objective: **Strengthen GP diabetes education**.

- *Target stakeholder*: Norwegian Medical Association (Den Norske Legeforening (DNLF)) and Association of General Practitioners (*Allmennlegeforeningen*) – later on other Nordic Medical Associations may also be relevant.
- *Tactics*: Ensure a dedicated class with focus on high-risk patients is incorporated into the annual pre- and post-gradual national courses in diabetes.

Strategic objective: **Improve clinical guidelines for key high-risk patients.**

- *Target stakeholder*: Norwegian guideline author group.
- *Tactics*: Translate key research findings into concrete suggestions on how to individualize guidelines for high-risk patients and on how different drug regimens may help solve key clinical issues such as non-adherence, therapeutic inertia and disease control variability in high-risk patients.

Strategic objective: **Secure high-risk patients access to innovation (e.g. reimbursement).**

- *Target stakeholder:* The Norwegian Medicines Agency (Legemiddelverket (LMV)) and the Norwegian Directorate of Health (Helsedirektoratet).
- *Tactics*: Identify and share patient subgroups with most attractive cost-benefit-ratio.

Strategic objective: **Enhance patient competences and empowerment.**

- *Target stakeholder:* Norwegian Diabetes Association (Diabetes Forbundet).
- *Tactics:* Norwegian Diabetes Association has written a letter of endorsement and granted financial resources to support the OMIT-initiative. Going forward, in close dialogue with the Norwegian Diabetes Association, the OMIT-study group will ensure key research findings

and key takeaways with relevance for patients will be communicated to patients, using both the webpage and the membership magazine of Norwegian Diabetes Association.

Strategic objective: **Improve political willingness to invest in high-risk patients.**

- *Target stakeholders:* Public media, Ministry of Health and Care Services and other political key decision makers.
- *Tactics:* Disseminate data and key takeaways related to current unmet needs in diabetes care but also communicate key conclusions regarding the effectiveness and cost-effectiveness of various treatments and interventions to build public and political awareness of inequality in diabetes outcomes and use evidence to shift focus from short-term budget impact to impact in the long-term on compiled disease life-cycle costs.

Strategic objective: **Ensure generated hypotheses are tested in prospective interventional studies.**

- *Target stakeholders:* Diabetes researchers in Norway and abroad and researchers involved in Norwegian general practice research network.
- *Tactics:* Ensure scientific data are presented at national and international scientific conferences and published in high-impact peer reviewed journals. In addition, identify hypotheses relevant to test in future prospective and interventional studies.

With this strategic approach, we aspire that the OMIT-project will help increase public awareness about unmet needs in current care, support patient empowerment by strengthening patient organization competences, influence policy makers to perform relevant and cost-effective investments, improve national guidelines and facilitate that the right patients get access to right treatments at the right time.

Competing interests

All authors have filled out and signed a “Disclosure of potential conflicts of interests”-form which can be reproduced upon request. E.S. Buhl is a previous employee of Novo Nordisk (2011-16) and has offered medical consulting and lectures to Novo Nordisk, Sanofi Aventis and MundiPharma. J.G. Cooper has received lecturing fees from Novo Nordisk, Sanofi Aventis, Eli Lilly, AstraZeneca, GSK. All other authors declare no conflicts of interests.

Author contributions

Together Dr. E.S. Buhl and Prof. Emeritus A.K. Jenum have initiated and driven the work related to drafting the overall OMIT research protocol, to applying for local ethics committee approval and to the process of performing the register linkages. Dr. E.S. Buhl is the primary investigator

(P.I.) on the OMIT-cohort study and Prof. M. M. Iversen has recently succeeded Prof. Emeritus Dr. A.K. Jenum in the role as Co-P.I.

Dr. K. Nøkleby, Dr. T. J. Berg, Prof. T. Iversen, Prof. T Hagen, Dr. J. Cooper, Prof. S. Sandberg and DrMsc. K. F. Løvaas have also provided substantial inputs to the overall OMIT-research protocol. After local ethics committee approval of the study-protocol, Dr. K. R. Richardsen, Prof. R. M. Nilsen and Prof. M. M. Iversen have joined the OMIT-study group, and co-P.I. Prof. M. M. Iversen has contributed substantially with the refinement of some of the research questions related to the protocol as well as to the strategic planning of the overall project. The first three Ph.D/Post.Doc.-research projects, out of six planned for the time being, originating from the protocol are in the process of being executed as a 1) PhD.-project focusing on complications in YOD patients (Dr. K. Tibballs based at University of Oslo (UiO) with Dr. E.S. Buhl as supervisor), 2) as a Post.Doc.-project assessing quality of care in elderly with T2D (Dr. R. B. Strandberg based at Western Norway University of Applied Sciences (HVL) with Prof. M.M. Iversen as supervisor) and 3) a Post.Doc.-project focusing on real-life drug effectiveness in YOD and elderly patients with T2D (candidate to be determined).

Dr. R. B. Forster has worked with the initial analyses and quality check of the data files and has first authored this cohort paper. All other researchers mentioned above each have contributed

significantly with the writing and review of this manuscript with last author and P.I. Dr. E. S. Buhl taking the role as corresponding author.

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Figure legends

Figure 1.

Provides an overview on how the OMIT project plan to study the defined three main research questions in three different main project streams (e.g.1. Burden of multi-morbidity, 2. Real-life drug utilization & performance and 3. Variability in disease control (quality of care)), where each of which will translate into several individual research subprojects/papers, each assessing individually defined exposures and groups of covariates in relation to individually defined primary and secondary outcomes.

Figure 2.

Overview of OMIT cohort construction, covered time-periods and overall data categories and co-variables.

Figure 3.

Number of OMIT cohort patients by source and year (first wave linkages).

The bars shown above only indicate the number of OMIT-patients reported to the NDR-A registry. Although reporting to the NDR-A registry did not start until 2008, please note that the

current cohort still includes some outpatient hospital data for the years 2006-2007. The green and transparent bars, placed in a front position, reflect the number of patients by year reported to NDR-A by hospital clinics, whereas violet bars, placed behind the green transparent bars, give the number of patients reported by year to the NDR-A by GPs. For the years 2012-14, please note that the ROSA4-data base contributed with additional 4,573 GP patients to the cohort which, however, are not accounted for in the shown violet bars.

Figure 4.

Venn diagram of overlap for total number of registered patients in OMIT cohort, with the first wave linkages, from the three different sources.

NB: When accounting for those overlaps, please note that the first wave cohort has enrolled 57,527 individual patients with type 2 diabetes.

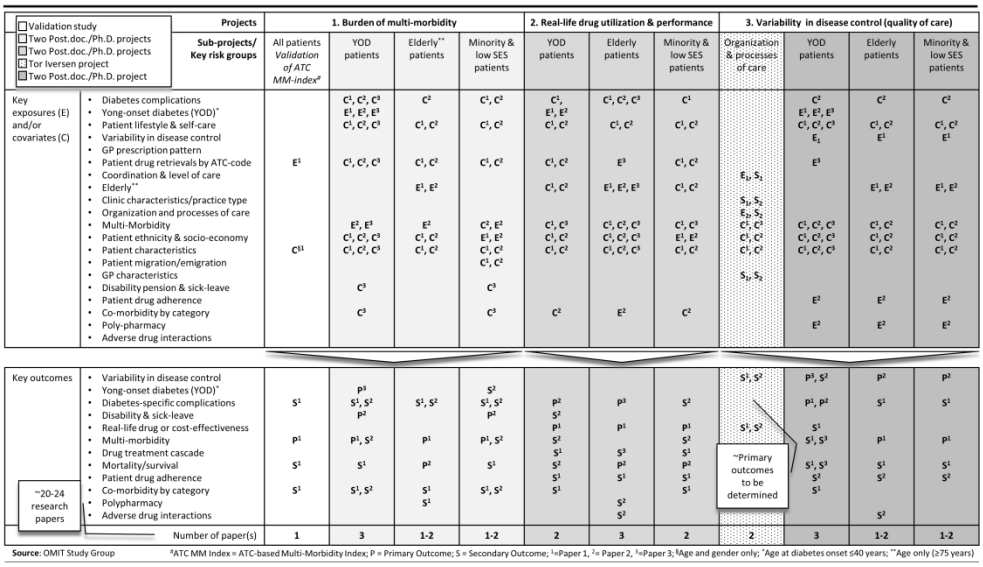
Figure 5.

Number of registered OMIT patients by year by county, standardised to total county population.

County legend, e.g. ISO-codes: 1. Østfold; 2 Akershus; 3 Oslo; 4 Hedmark; 5 Oppland; 6 Buskerud; 7 Vestfold; 8 Telemark; 9 Aust-Agder; 10 Vest-Agder; 11 Rogaland; 12 Hordaland; 14 Sogn og Fjordane; 15 Møre og Romsdal; 16 Sør-Trøndelag*; 17 Nord-Trøndelag*; 18 Troms; 20 Finnmark.

* In 2019 Nør- and Sør-Trøndeag were combined in to a single county, Tøndelag, ISO-code 50.

§ Regions that contributed to data in the ROSA4 study in 2014: Rogaland, Oslo, Salten - a region in Nordland - , Akershus and Hordaland.



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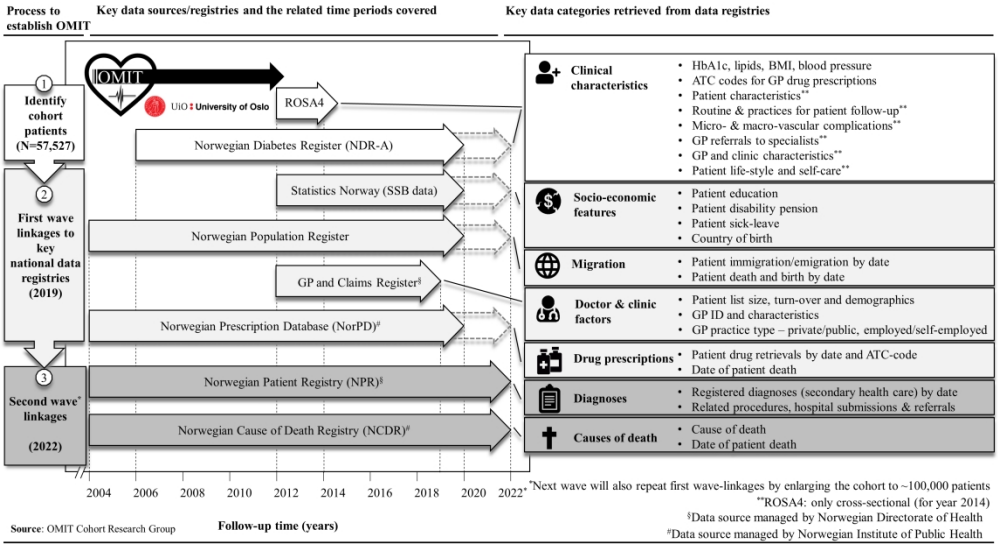

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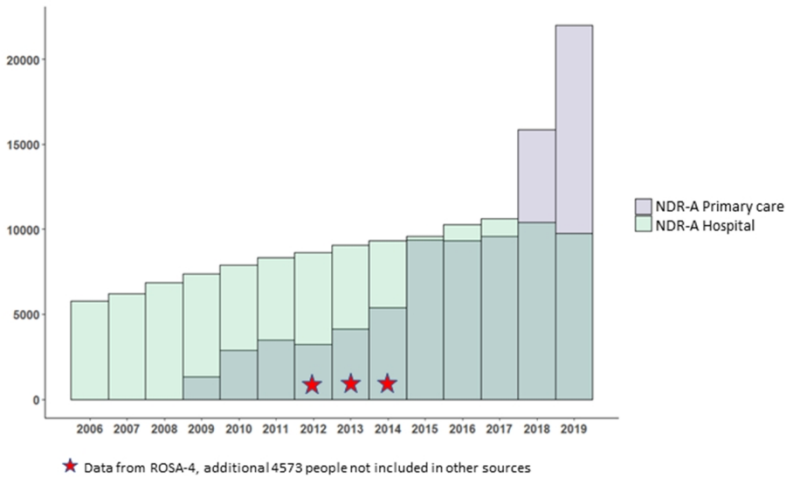

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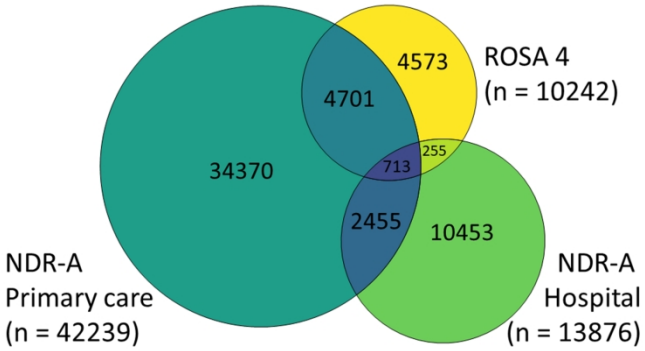

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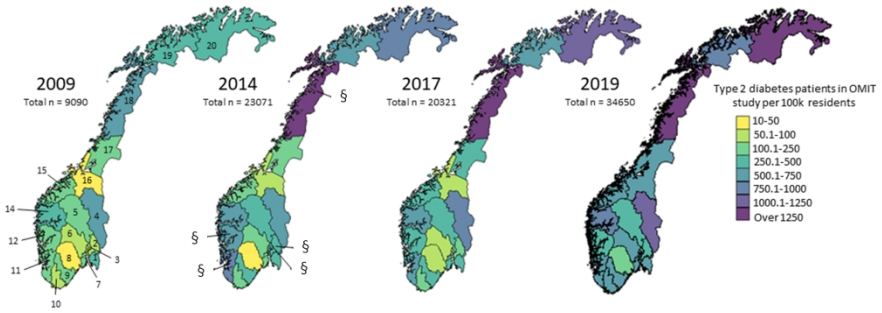

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Number of registered OMIT patients by year by county, standardised to total county population.
County legend, e.g. ISO-codes: 1. Østfold; 2 Akershus; 3 Oslo; 4 Hedmark; 5 Oppland; 6 Buskerud; 7 Vestfold; 8 Telemark; 9 Aust-Agder; 10 Vest-Agder; 11 Rogaland; 12 Hordaland; 14 Sogn og Fjordane; 15 Møre og Romsdal; 16 Sør-Trøndelag*; 17 Nord-Trøndelag*; 18 Troms; 20 Finnmark.
* In 2019 Nør- and Sør-Trøndeag were combined in to a single county, Tøndelag, ISO-code 50.
§ Regions that contributed to data in the ROSA4 study in 2014: Rogaland, Oslo, Salten - a region in Nordland - , Akershus and Hordaland.

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