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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)

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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V4 01/07/2021

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

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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 $7.58 \pm 1.5\%$

V4 01/07/2021

Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
(59.4 ± 16.28 mmol/mol), mean BMI and blood pressure is 30.2 ± 5.9 kg/m² and $135 \pm 16.1/78 \pm 9.8$ 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.

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

- 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.

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V4 01/07/2021

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

Introduction

Background

The prevalence of Type 2 diabetes (T2D) is increasing worldwide, and so is the burden of related vascular complications and death¹. Diabetes is a major cause of cardiovascular disease, blindness², chronic kidney disease³, diabetic foot ulcers⁴ and limb amputations⁵. Beyond the immense reduction in quality of life, these complications lead to reduced labour market participation and inflict a considerable burden on the global economy⁶.

Although timely and efficacious interventions can improve patient outcomes and reduce the economic burden⁷, 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 Association⁹ and Norwegian Directorate of Health¹⁰ 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 participate¹¹. 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),

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

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3 2) elderly above 75 years, 3) ethnic minorities, and 4) patients with low socio-economic status.

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6 Moreover, the strategies suggested by the guidelines provide only a vague guidance as to how
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10 diabetes care should be customized and organized in a general practice setting and fail to
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13 deliver clear recommendations on how to address a broad range of key barriers to good disease
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16 control for vulnerable groups¹². Consequently, we need more evidence to better understand the
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19 current unmet needs and evidence documenting the effectiveness, cost-effectiveness and safety
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22 of various treatments and clinical procedures in relation to how they may impact both disease
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25 control and harder disease outcomes in high-risk patients. As high-risk patients have proven
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28 difficult to include in prospective interventional trials, instead we see a great opportunity to
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31 employ non-interventional, observational data already present in various high-quality national
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34 registries.
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38 The “Outcomes & Multi-morbidity in Type 2 Diabetes” (OMIT) cohort, which is based on multiple
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41 linkages between various Norwegian population-based registries, was established to support
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44 non-interventional observational studies of high-risk patients with T2D treated in general
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47 practice, in out-patient hospital clinics, or by shared care. The first wave of the OMIT cohort
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49
50 focus primarily on the following key high-risk groups: (1) young onset diabetes (YOD - T2D prior
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53 to age 40), (2) elderly patients (>75 years of age), (3) non-western ethnic minorities (i.e. non-
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V4 01/07/2021

1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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3 western immigrants excluding Eastern European immigrants), and (4) low socio-economic status
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6 (SES) patients. Low SES defined here as having only primary level education. The OMIT-cohort
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9 will also have data to support more refined SES-definitions accounting for personal and
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13 household income, as well as employment status (for those in working age).
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19 *OMIT research questions*

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22 Currently, we have three broad research questions:

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

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32 (2) How do newer anti-diabetic drugs perform in terms of real-life effectiveness (e.g. as opposed
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34 to drug efficacy, which can be measured only in randomized clinical trials), cost-effectiveness,
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36 safety and adherence in high-risk groups?
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42 (3) What are the causes and effects of diabetes control variability on intermediate and harder
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44 disease outcomes, and how is the organization of diabetes care related to these outcomes?
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48 For the intended investigation of key high-risk patient groups, we have further defined the
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50 following endpoints:
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1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)

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3 *Primary endpoint:* multi-morbidity measured according to the weighted prescription (Rx) Risk

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6 Comorbidity Index (RRCI), calculated based on recorded Anatomical Therapeutic Chemical

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10 (ATC) codes¹³.

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13 *Secondary outcomes:*

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16 (1) Co-morbidity, ATC-code based estimates of key morbidity categories; (2) early onset

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19 diabetes; (3) mortality (4) diabetes-specific and macrovascular complications (5) drug adherence

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22 (6) drug treatment cascade (7) drug effectiveness and cost-effectiveness (8) polypharmacy and

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25 risk of potentially adverse drug interactions (9) quality of care/disease control (e.g. risk factor

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28 variability) (10) disability pension/sick

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31 leave.

32 33 34 35 36 37 38 39 **Cohort description**

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43 *Patient enrolment and sample size*

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46 OMIT eligible patients are identified from the Norwegian Diabetes Register for Adults (NDR-A) or

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49 the Rogaland-Oslo-Salten-Akershus-Hordaland (ROSA 4) study, covering the time-period from

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52 2006 to 2019. Subsequently, these data sources are linked to the Norwegian Prescription

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55 Database for dispensed medications, the Norwegian Population Register for data on death and

V4 01/07/2021

1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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3 migration, Statistics Norway for data on socio-economic factors and ethnicity and the Norwegian
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6 Directorate of Health for data on the general practices and clinical procedures involved in the
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10 care of cohort patients.

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16 **Figure 1** provides an overview of the different cohort-data sources, the time-periods covered with
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18
19 the first and second wave register linkages and the different data categories made available for
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21
22 the included cohort patients. First wave linkages involves data until December 31st 2019
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26 whereas second wave linkages will extend covered time period until December 31st 2022 and
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29 supplement the cohort with additional data from the Norwegian Patient Registry and Norwegian
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32 Cause of Death Registry.

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38 The NDR-A was established in 2005 with the aim of improving the quality of treatment of people
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41 with diabetes in Norway¹⁴. The registry has included out-patient hospital data since 2006,
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44 although reporting did not start until 2008. Primary care data has been included since 2009.
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48 Since then, the number of included patients in NDR-A has grown steadily. However, mainly due
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51 to requirements of written informed consent, enrolment was low in the early years, especially for
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54 people with T2D. In response, the ROSA 4 study was created to secure access to representative
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1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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3 data on patients with diabetes from diverse clinical settings. ROSA4 is a population-based cross-
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6 sectional survey conducted in 2015 (but based on data from the time period 2012-2014) that
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9 included people with T2D identified by general practitioners (GP) that agreed to participate. A
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12 total of 282 GPs, 77% of those invited, and 10,248 patients were enrolled¹⁵.
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19 As a natural extension of the past initiatives, the “Outcomes & Multi-morbidity in Type 2
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22 Diabetes” (OMIT) project has now combined data from the NDR-A and ROSA4. OMIT will carry
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25 forward previous research efforts focusing on the quality of care for people with T2D in Norway,
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28 although this time with a dedicated focus on high-risk groups often omitted from randomized
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31 clinical trials (hence the acronym OMIT).
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38 **Figure 2** shows the number of OMIT cohort patients by source and year, as well as patient
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41 enrolment over time organized by hospital and primary care sources. **Figure 2** also shows that
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44 ROSA4 contributed data in the time-period 2012-2014, although some ROSA4 patients may also
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47 have been in the NDR-A prior to and after these years. The ROSA4 study comprises longitudinal
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50 laboratory and drug prescription data from 2012-2014 and cross-sectional data on other patient
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53 characteristics from 2014. When considering the overlap with the NDR-A, ROSA4 delivered an
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V4 01/07/2021

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

2 additional 4,573 patients to the OMIT cohort. Going forward, we expect the cohort to grow

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6 further as a more GPs report to the register. Recent changes in national regulations have made

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9 it possible for national health registers to apply for inclusion of patients without informed consent

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12 if patients have not proactively put forward a request to be excluded¹⁶. In addition, The

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15 Norwegian Health Economics Administration (HELFO) has recently introduced a payment per

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18 registered patient to GPs who submit clinical data to the NDR-A. This is likely to accelerate GP

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21 reporting further. Consequently, the OMIT cohort is expected to grow to ~100,000 patients with

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24 T2D in 2022 (second wave linkages).

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28 Between 2006 and 2019, a total of 57,527 individuals have been identified from the NDR-A and

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31 ROSA4, and included in OMIT. This includes 10,242 people within the ROSA4 study, 42,239

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34 people with data in the NDR-A primary care database and 13,876 with data in the NDR-A

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37 hospital database. There is substantial overlap between the databases (**Figure 3**). For the high-

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40 risk groups, the current OMIT cohort includes data for about 6,500 YOD patients, 15,500 elderly

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43 (>75 years), about 9,000 non-western ethnic minority patients and 20,500 patients with primary

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48 education only.

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

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3 **Figure 4** illustrates development in the national coverage of the cohort via a series of maps,
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6 identifying the different counties of Norway. The fill colour is indicative of the county's total
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9 number of registered patients in OMIT, standardized to county population. In 2009, several
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12 counties had low coverage, such as the counties Sør-Trøndelag and Telemark, but this has
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15 improved over time to all counties having over 100 T2D patients per 100,000 residents included
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18 in the OMIT cohort in 2019, and several counties have over 1000 patients per 100,000. Although
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21 roughly one-third of GPs reported patients to the NDR-A in 2019, the OMIT-cohort at present
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24 only includes about 20% of the T2D population in Norway¹⁷. However, all counties are
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27 represented, and thus it offers good reliability when studying populations that may differ
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31 regionally.
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34 *Patient follow-up*

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38 The first wave linkages for the OMIT study included all data in NDR-A and ROSA4 up until the
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41 end of 2019. Patients are generally followed up at least once per year as one annual diabetes
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44 control is recommended as the minimum in general practice and GPs now receive a payment
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47 per patient for performing annual follow-up and reporting data to the NDR-A. In the current
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51 cohort, the median follow-up time between the first and final HbA1c measures is 2 years, with an
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V4 01/07/2021

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

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%)

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

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

V4 01/07/2021

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

2
3 comprehensiveness of the cohort and prove solid ground for future studies focusing on mortality
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6 related outcomes.
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10 11 12 *Data sources and categories*

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15
16 *NDR-A and ROSA4*: Data gathered from NDR-A and ROSA4 databases include a wide array of
17
18 demographic and clinical data. These data include year of birth, sex and regional location,
19
20 diabetes variables including year of diagnosis and HbA1c measures, as well as blood pressure
21
22 and lipid measurements and prescribed medications. We have also collected important vascular
23
24 outcomes such as retinopathy, cardiovascular disease, nephropathy and markers of neuropathy
25
26 that include evidence of foot ulcers, monofilament foot examinations and pulse testing. **Table 1**
27
28 provides an overview of some of the important clinical variables collected from NDR-A and
29
30 ROSA4.
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41
42 *Statistics Norway (SSB)*: Data gathered from Statistics Norway mainly cover socio-economic
43
44 factors, including education, disability income, sick-leave and country of birth.
45
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49 *Norwegian Population Register (NPR)*: The data from NPR will provide detailed information on
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51 migration of the patients within the study, including dates for immigration and/or emigration and
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53 death.
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1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)

2
3 *Norwegian Prescription Database (NorPD)*: Data from the NorPD represent all dispensed

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5
6 prescriptions by date and ATC-codes for each participant. The OMIT cohort also obtains date of
7
8
9 death from NorPD.

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11
12 Further, based on ATC codes we will construct and validate an ATC-code based multi-morbidity
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14
15 score¹³, which will then serve as an individual measure applicable as either an exposure or an
16
17
18 outcome in subsequent research studies.
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20

21
22 *Norwegian Directorate of Health*. The Norwegian Directorate of Health manages several national
23
24
25 registers, including the medical claims register (KUHR) and the Health Personnel Register
26
27
28 (HPR), from which we will receive data on GPs and features of their clinical practices. This
29
30
31 includes patient list size, waiting list size, patient turnover data and demographics. GP
32
33
34 characteristics include specialist status and whether the GP is salaried or self-employed, as well
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36
37 as an overview of the procedure-related payments and diagnoses recorded by the GP, enabling
38
39
40 analyses of health economic outcomes.
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44 45 Findings to date

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47
48 In 2019, the average age of the OMIT cohort was 67.4±13.2 years with an average T2D duration
49
50
51 of 12.3±8.3 years (**Table 1**). The mean HbA1c for the whole cohort through the study period was
52
53
54 7.58±1.5% (59.4±16.28 mmol/mol), BMI was 30.2±5.9 kg/m² and blood pressure 135±16.1/78±9.8
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V4 01/07/2021

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

2 mmHg. A total of 10.1% of the cohort had evidence of retinopathy, 21% with coronary heart
3
4 disease and 6.7% had had a stroke. Missing data varied greatly depending on the variable, with
5
6
7 only 2.5% of the cohort missing HbA1c measures, while up to 52.6% were missing urinary
8
9
10
11
12
13 albumin creatinine ratio (ACR).

14
15
16 **Table 1** shows only the main diabetes related variables by source, and how data from different
17
18 sources can be mutually supplementary to reduce the impact of missing data obtained from a
19
20 single source. For example, 14.4% were missing blood pressure measurements from NDR-A
21
22 hospital records, but due to the higher coverage by the NDR-A primary care records, only 8.2%
23
24 of the whole cohort have missing blood pressure readings. Even though urinary ACR currently
25
26 has a high amount of missing data, we will have the advantage of a large sample size in addition
27
28 to a broad range of other co-variables (including estimates of glomerular filtration rate (eGFR)
29
30 (calculated by use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)
31
32 equations using serum creatinine measures¹⁸)) which will allow imputation for missing ACR
33
34 values.
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48 The ROSA4 study, a seminal part of OMIT, has already published many studies related to T2D
49
50 care in Norway, including findings that non-Western ethnic minorities are diagnosed with T2D at
51
52 an earlier age than Westerners and are less likely to achieve target HbA1c measures¹⁹. An early
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1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
2
3 study demonstrated modest improvements in diabetes related risk markers from 2005 to 2014 in
4
5
6 general practice, including HbA1c, blood pressure and lipids, but revealed suboptimal screening
7
8
9 for microvascular complications, such as nephropathy¹⁵. Another ROSA4 study indicated that
10
11
12 point-of-care HbA1c testing in general practice was linked to better glycaemic regulation in
13
14
15 patients with T2D²⁰. Finally, ROSA4 has reported that GP adherence to recommended standard
16
17
18 follow-up procedures in T2D was related to both clinic structure and workload²¹.
19
20
21

22 Now that we have expanded the ROSA4 study, we are optimistic the OMIT cohort can further
23
24
25 drive the work to enhance our knowledge about how we treat and care for patients with T2D in
26
27
28 Norway. This work will position us to put forward concrete and tangible evidence-based
29
30
31 recommendations on how diabetes care may be improved, with a special attention to high-risk
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34 patients.
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42 **Strengths and limitations**

43 *Strengths*

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45
46 The OMIT cohort is the first dedicated T2D cohort in Norway constructed from high-quality
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48
49 national registry data that includes patients from all counties, with increasing representativeness
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51
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53 over time. Further, OMIT provides separate data from both out-patient clinics and general
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V4 01/07/2021

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

2 practices which enables studies of potential differences between these two patient populations.

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6 OMIT will support detailed analyses that will generate both nationally generalizable as well as

7
8
9 internationally relevant findings. This surpasses the ability of studies such as HUNT and Tromsø

10
11
12 Study, both of which are regionally restricted, rely partially on self-reported diabetes diagnoses

13
14
15 and have a lower sample size of patients with T2D²¹. Most OMIT data are longitudinal, which

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17
18 allows us to assess exposures at a time point prior to the defined outcomes. Also, OMIT will

19
20
21 provide a basis for studying causes and effects of multi-morbidity rather than only traditional risk

22
23
24 factors (e.g. hypertension, hyperglycaemia, hyperlipidaemia etc.). We currently have an

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26
27 extensive dataset that provides us with a full description of clinical features, socio-demographics,

28
29
30 economy and ethnicity, drug prescriptions and drug retrievals, delivered care and treatment

31
32
33 processes, and organizational factors including collaborations between primary and specialist

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35
36 care. Together these data provide a strong basis for assessing possible relations between all the

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38
39 defined exposures and outcomes and to correct for a multitude of confounders. In order to

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41
42 explore potential causal factors, we will draw Directed Acyclic Graphs (DAGs) prior to analyses

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44
45 to identify true confounders to be adjusted for, in line with statistical methods developed to

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47
48 support causal inference in observational data.

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

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3 *Limitations*

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6 In this first wave of linkage, the majority of patients in the cohort are included from hospital
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9
10 outpatient clinics which are likely to differ from patients cared for only in general practice, a
11
12
13 condition reflected by a mean HbA1c for the whole cohort as high as 7.58% (59.4±16.28
14
15
16 mmol/mol). Further, in the current OMIT cohort there may be a risk of selection bias, particularly
17
18
19 in the earlier years in the NDR-A data reported by GPs, as those willing to participate early on
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21
22 may have provided a higher level of care. This type of bias can mean there is lower external
23
24
25 validity of primary care NDR-A data reported earlier. We plan to assess the overall
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27
28 representativeness of these data by use of the ROSA4-population which is considered more
29
30
31 representative for Norwegian general practice. Some variables have high levels of missing data,
32
33
34 and follow-up time-periods vary between data sources and within patients. Thus, it may be
35
36
37 relevant to perform analysis of potential selection bias due to self-selection and missing data.
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45 **Data Availability Statement**

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49 All OMIT data are stored and analysed on the platform for safe storage of sensitive data (TSD)
50
51
52 at the University of Oslo until 2035. In support of collaborative research projects, access can be
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54
55 granted after approval by the OMIT-study group, the Regional Committee for Medical and Health
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V4 01/07/2021

1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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3 Research Ethics and the data owner at the University of Oslo. Project requests can be directed
4
5
6 to Esben Selmer Buhl at the Department of General Practice, Institute of Health and Society,
7
8
9 University of Oslo (email: e.s.buhl@medisin.uio.no)
10
11
12

13 Further details

14 *Funding*

15
16
17 The first phase of linkages has been funded by the University of Oslo. Currently, senior
18
19 researchers and one postdoctoral position (Western Norway University of Applied Sciences
20
21
22 (HVL), Norway) are funded by their home institutions (for senior researchers: see author
23
24
25 affiliation list). The cohort is also funded by The Norwegian Diabetes Association
26
27
28 (Diabetesforbundet) and the Norwegian Research Fund for General Practice (Allmenntmedisinsk
29
30
31 forskningsfond), with the latter also funding one PhD-student (University of Oslo (UiO), Norway).
32
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38 *Ethics and ethics approval*

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40
41 The project has obtained ethical approval from Regional Committees for Medical Research
42
43
44 Ethics - South East Norway (REC South East (Ref# 74012)) and is approved by the Data
45
46
47 Protection Official/Officer at UiO. Data linkage began in mid-2020 for the years 2006-2019. After
48
49
50 the final linkages of data from all registers, all researchers are not in any way be able to identify
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52
53 individual patients. We have reduced the number of categories for variables (data minimization)
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1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)

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3 to secure a sufficient number in each cell so that patients cannot be retrospectively identified.

4
5
6 Individual researchers will only have access to variables relevant for their research questions,

7
8
9 and only after granted approval from REC South East.

10 11 12 *Patient and Public Involvement*

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14
15 The OMIT-study has received a letter of endorsement from the Norwegian Diabetes Association

16
17 in addition to financial support, and key senior researchers from the OMIT-study group, including

18
19 Prof. Emeritus Anne Karen Jenum, over the years with the ROSA4-study have had a long-

20
21
22 standing close collaboration with Norwegian Diabetes Association, which we aspire to continue

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24
25 with the OMIT-initiative.

26
27
28 To secure that the current research project will result in tangible and quantifiable improvements

29
30
31 in the clinical care of high-risk patients with T2D, in alignment with patient preferences and

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33
34 identified unmet needs, we have identified the following key strategic objectives and the

35
36
37 related target stakeholder and tactics:

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46 *Strategic objective: Strengthen GP diabetes education.*

V4 01/07/2021

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

- *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.**

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

- 2
- 3 • *Target stakeholder:* Norwegian Diabetes Association (Diabetes Forbundet).
- 4
- 5
- 6 • *Tactics:* Norwegian Diabetes Association has written a letter of endorsement and granted
- 7
- 8
- 9 financial resources to support the OMIT-initiative. Going forward, in close dialogue with the
- 10
- 11 Norwegian Diabetes Association, the OMIT-study group will ensure key research findings
- 12
- 13 and key takeaways with relevance for patients will be communicated to patients, using both
- 14
- 15 the webpage and the membership magazine of Norwegian Diabetes Association.
- 16
- 17
- 18
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- 21

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

- 23
- 24
- 25
- 26 • *Target stakeholders:* Public media, Ministry of Health and Care Services and other political
- 27
- 28 key decision makers.
- 29
- 30
- 31
- 32 • *Tactics:* Disseminate data and key takeaways related to current unmet needs in diabetes
- 33
- 34 care but also communicate key conclusions regarding the effectiveness and cost-
- 35
- 36 effectiveness of various treatments and interventions to build public and political awareness
- 37
- 38 of inequality in diabetes outcomes and use evidence to shift focus from short-term budget
- 39
- 40 impact to impact in the long-term on compiled disease life-cycle costs.
- 41
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48 ***Strategic objective:* Ensure generated hypotheses are tested in prospective interventional**

49

50 **studies.**

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V4 01/07/2021

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

- *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.

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

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3 *Author contributions*

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6
7 Together Dr. E.S. Buhl and Prof. Emeritus A.K. Jenum have initiated and driven the work related
8
9
10 to drafting the overall OMIT research protocol, to applying for local ethics committee approval
11
12
13 and to the process of performing the register linkages. Dr. E.S. Buhl is the primary investigator
14
15
16 (P.I.) on the OMIT-cohort study and Prof. M. M. Iversen has recently succeeded Prof. Emeritus
17
18
19 Dr. A.K. Jenum in the role as Co-P.I.

20
21
22
23 Dr. K. Nøkleby, Dr. T. J. Berg, Prof. T. Iversen, Prof. T Hagen, Dr. J. Cooper, Prof. S. Sandberg
24
25
26 and DrMsc. K. F. Løvaas have also provided substantial inputs to the overall OMIT-research
27
28
29 protocol. After local ethics committee approval of the study-protocol, Dr. K. R. Richardsen, Prof.
30
31
32 R. M. Nilsen and Prof. M. M. Iversen have joined the OMIT-study group, and co-P.I. Prof. M. M.
33
34
35 Iversen has contributed substantially with the refinement of some of the research questions
36
37
38 related to the protocol as well as to the strategic planning of the overall project. The first three
39
40
41 Ph.D/Post.Doc.-research projects, out of six planned for the time being, originating from the
42
43
44 protocol are in the process of being executed as a 1) PhD.-project focusing on complications in
45
46
47 YOD patients (Dr. K. Tibballs based at University of Oslo (UiO) with Dr. E.S. Buhl as supervisor),
48
49
50 2) as a Post.Doc.-project assessing quality of care in elderly with T2D (Dr. R. B. Strandberg
51
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53 based at Western Norway University of Applied Sciences (HVL) with Prof. M.M. Iversen as
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V4 01/07/2021

1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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3 supervisor) and 3) a Post.Doc.-project focusing on real-life drug effectiveness in YOD and
4
5
6 elderly patients with T2D (candidate to be determined).
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8

9
10 Dr. R. B. Forster has worked with the initial analyses and quality check of the data files and has
11
12 first authored this cohort paper. All other researchers mentioned above each have contributed
13
14 significantly with the writing and review of this manuscript with last author and P.I. Dr. E. S. Buhl
15
16
17 taking the role as corresponding author.
18
19
20

21 *Acknowledgements*

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25
26 We would like to extend our gratitude to the medical and research staff that have supported the
27
28
29 work of ROSA4 and NDR-A, as well as the patients and doctors that have contributed data. We
30
31
32 thank the Norwegian Diabetes Association (Diabetesforbundet) and for the Lillian and Werner
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35 Næss Scholarship and research fund for supporting authors associated with OMIT.
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Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)

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V4 01/07/2021

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V4 01/07/2021

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

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.

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

2
3 Figure 3.

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

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13 NB: When accounting for those overlaps, please note that the first wave cohort has enrolled

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16 57,527 individual patients with type 2 diabetes.
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28 Figure 4.

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32 *Number of registered OMIT patients by year by county, standardised to total county population.*
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36 County legend, e.g. ISO-codes: 1. Østfold; 2 Akershus; 3 Oslo; 4 Hedmark; 5 Oppland; 6

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38 Buskerud; 7 Vestfold; 8 Telemark; 9 Aust-Agder; 10 Vest-Agder; 11 Rogaland; 12 Hordaland;

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42 14 Sogn og Fjordane; 15 Møre og Romsdal; 16 Sør-Trøndelag*; 17 Nord-Trøndelag*; 18 Troms;

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45 20 Finnmark.
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49 * In 2019 Nør- and Sør-Trøndeag were combined in to a single county, Tøndelag, ISO-code 50.
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V4 01/07/2021

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3 § Regions that contributed to data in the ROSA4 study in 2014: Rogaland, Oslo, Salten - a

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6 region in Nordland - , Akershus and Hordaland.
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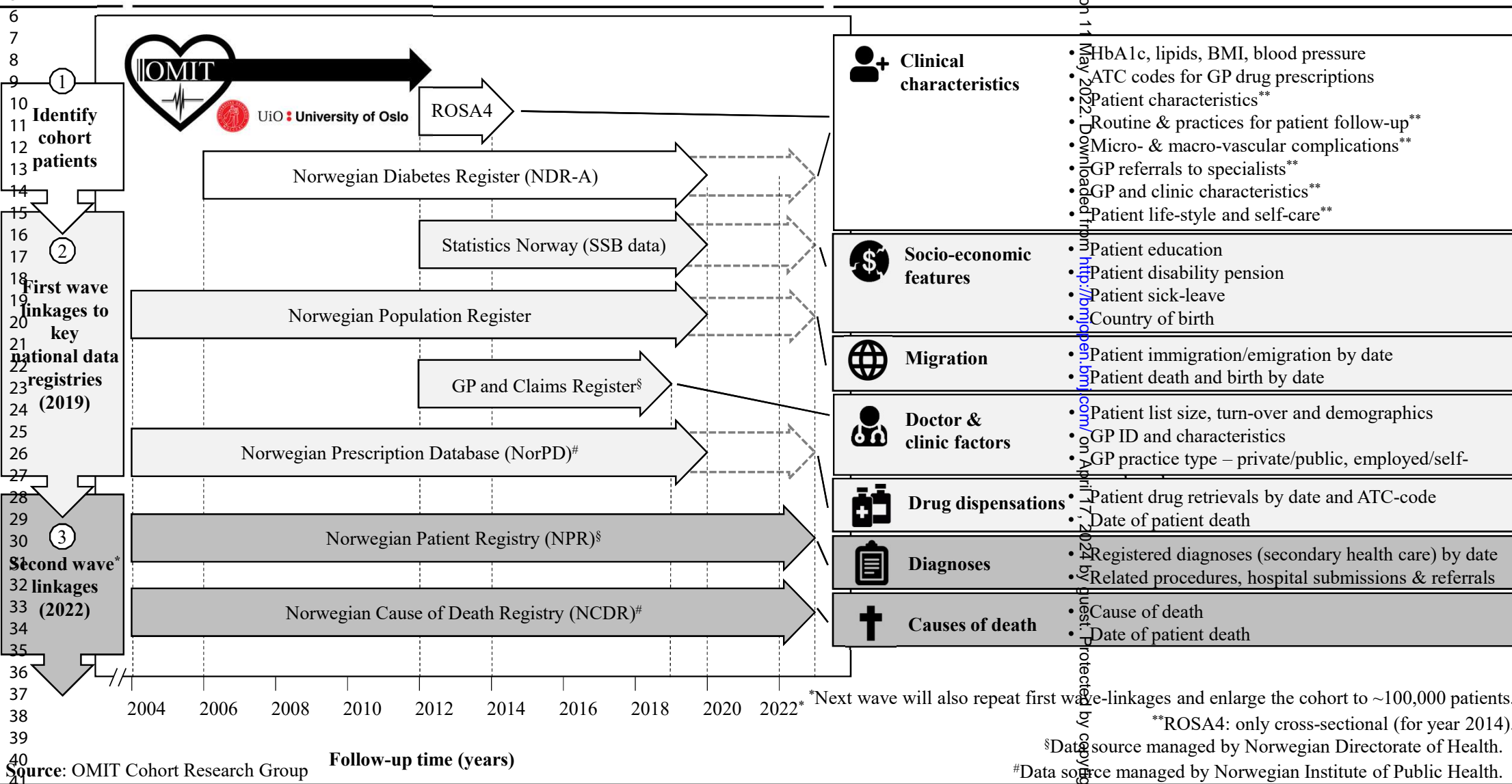
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Figure 1

Process to build OMIT

Key data sources/registries and the related time periods covered

Key data categories retrieved from data registries



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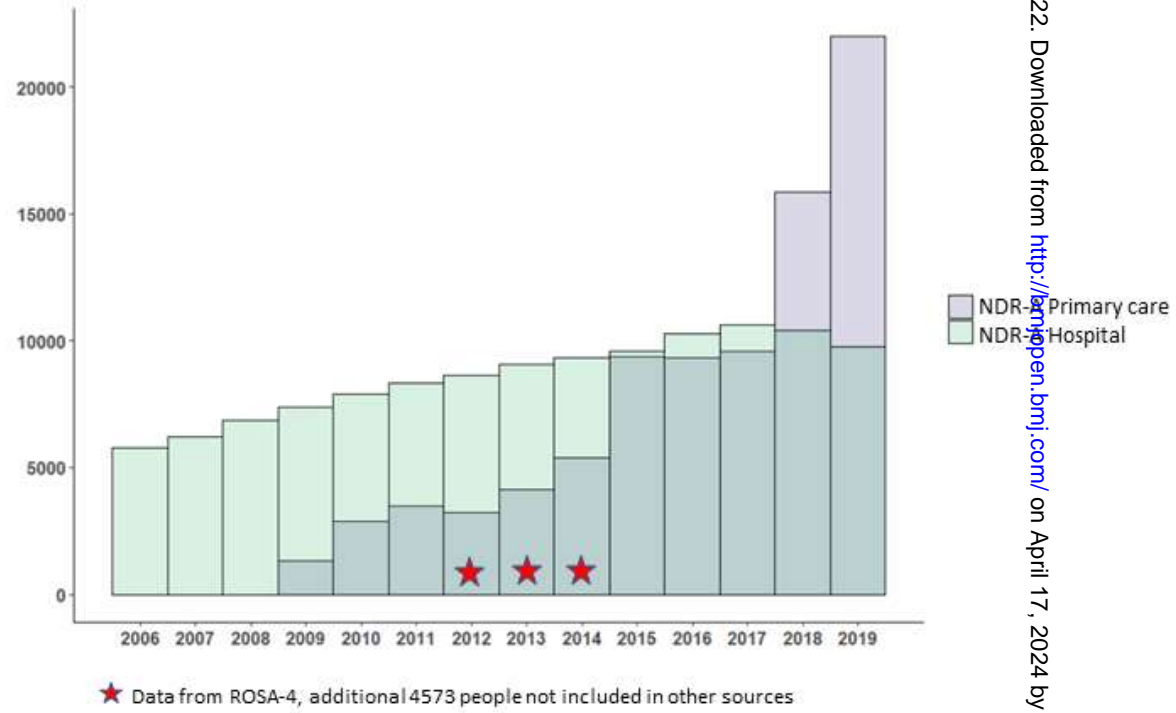
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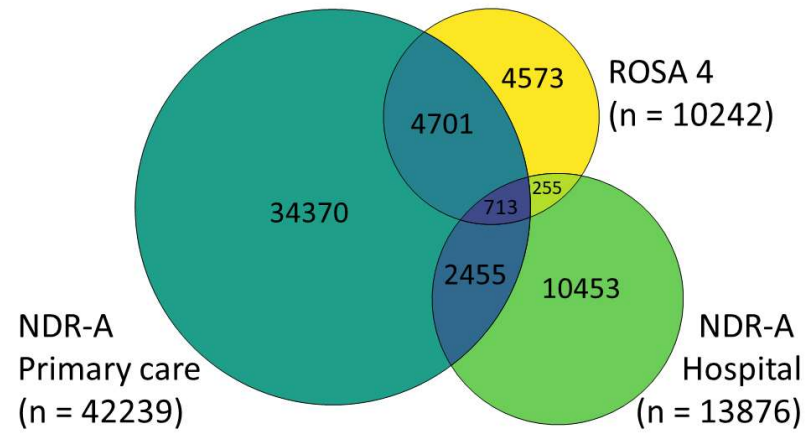
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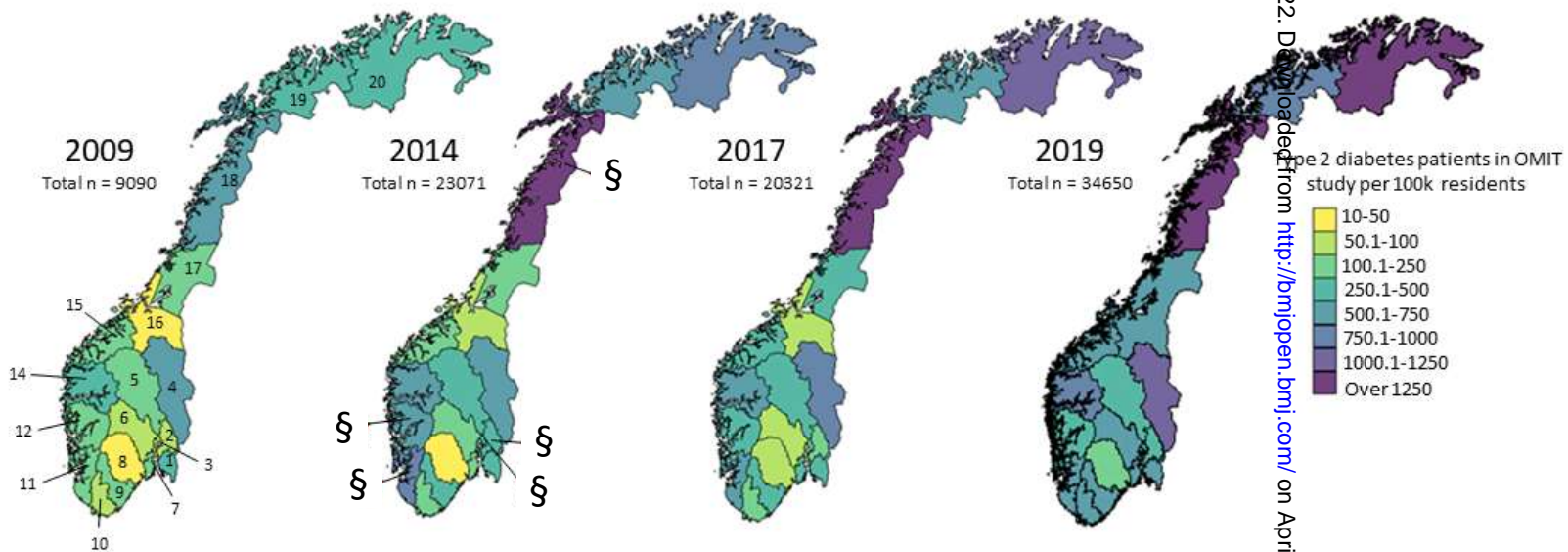


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Figure 3



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3 **Figure 4**

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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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Primary Subject Heading:	Diabetes and endocrinology

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Secondary Subject Heading:	Epidemiology, General practice / Family practice
Keywords:	DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, PRIMARY CARE, General diabetes < DIABETES & ENDOCRINOLOGY





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

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

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

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6 24 *: Senior author and primary investigator on the OMIT-cohort.

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12 26 Word count: 3,999 (excl. title page, abstract, tables, acknowledgements, contributions,

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15 27 references and figure legends)

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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%

V5 19/12/2021

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

(59.4±16.3 mmol/mol), mean BMI and blood pressure is 30.2±5.9 kg/m² 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.

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

- 61 • OMIT is expected to grow further and to offer even more exhaustive data via repeated
- 62 linkages performed every third to fifth year.
- 63 • OMIT may not be fully representative for Norwegian general practice, especially in the
- 64 earlier years, as many of the patients then were included from hospital outpatient clinics
- 65 and are likely to differ from patients cared for only in general practice.
- 66 • There may be a risk of self-selection bias, especially for the earlier years, as those GPs
- 67 willing to report data early on may have provided a higher level of care.

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V5 19/12/2021

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

71 Introduction

72 *Background*

73 The prevalence of Type 2 diabetes (T2D) is increasing worldwide, and so is the burden of
74 related vascular complications and death¹. Diabetes is a major cause of cardiovascular disease,
75 blindness², chronic kidney disease³, diabetic foot ulcers⁴ and limb amputations⁵. Beyond the
76 immense reduction in quality of life, these complications lead to reduced labour market
77 participation and inflict a considerable burden on the global economy⁶.

78 Although timely and efficacious interventions can improve patient outcomes and reduce the
79 economic burden⁷, the evidence for current drug regimens is often limited in patients with
80 greater needs as they are often omitted from clinical trials. Clinical guidelines from the European
81 Association for the Study of Diabetes (EASD)⁸, the American Diabetes Association⁹ and
82 Norwegian Directorate of Health¹⁰ provide some guidance on how to manage diabetes
83 treatments and disease control targets based on an individualized approach. However, a key
84 weakness is the guidelines are based on results from trials where only 3.5–35.7% of patients in
85 daily clinical practice would have been eligible to participate¹¹. Therefore, the generated results
86 from these trials may not be generalizable for the majority of patients, especially vulnerable
87 groups such as 1) those with young onset diabetes (T2D prior to age 40), 2) elderly above 75

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

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3 88 years, 3) ethnic minorities, and 4) patients with low socio-economic status. Moreover, the
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6 89 strategies suggested by the guidelines provide only a vague guidance as to how diabetes care
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10 90 should be customized and organized in a general practice setting and fail to deliver clear
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13 91 recommendations on how to address a broad range of key barriers to good disease control for
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16 92 vulnerable groups¹². Consequently, we need more evidence to better understand the current
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19 93 unmet needs and evidence documenting the effectiveness, cost-effectiveness and safety of
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22 94 various treatments and clinical procedures in relation to how they may impact both disease
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25 95 control and harder disease outcomes in high-risk patients. As high-risk patients have proven
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28 96 difficult to include in prospective interventional trials, instead we see a great opportunity to
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32 97 employ non-interventional, observational data already present in various high-quality national
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35 98 registries.

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38 99 The “Outcomes & Multi-morbidity in Type 2 Diabetes” (OMIT) cohort, which is based on multiple
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41 100 linkages between various Norwegian population-based registries, was established to support
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45 101 non-interventional observational studies of high-risk patients with T2D treated in general
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48 102 practice, in outpatient hospital clinics, or by shared care. The first wave of the OMIT cohort focus
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51 103 primarily on the following key high-risk groups: (1) young onset diabetes (YOD - T2D prior to age
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54 104 40), (2) elderly patients (>75 years of age), (3) non-western ethnic minorities (i.e. non-western
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V5 19/12/2021

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

105 immigrants excluding Eastern European immigrants), and (4) low socio-economic status (SES)

106 patients. Low SES defined here as having only primary level education. The OMIT-cohort will

107 also have data to support more refined SES-definitions accounting for personal and household

108 income, as well as employment status (for those in working age).

109

110 *OMIT research questions*

111 Currently, we have three broad research questions:

112 (1) How does multi-morbidity interact with diabetes development and care, and how is it related

113 to intermediate (e.g HbA_{1c}, LDL and/or blood pressure) and harder disease outcomes (e.g.

114 diabetes-specific complications and/or death)?

115 (2) How do newer anti-diabetic drugs perform in terms of real-life effectiveness (e.g. as opposed

116 to drug efficacy, which can be measured only in randomized clinical trials), cost-effectiveness,

117 safety and adherence in high-risk groups?

118 (3) What are the causes and effects of diabetes control variability on intermediate and harder

119 disease outcomes and how is the organization of diabetes care related to these outcomes?

120

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

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

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

134 Cohort description

135 *Data sources and categories*

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

V5 19/12/2021

1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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4 138 including year of diagnosis and HbA_{1c} measures, as well as blood pressure and lipid
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7 139 measurements and prescribed medications. We have also collected important vascular
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10 140 outcomes such as retinopathy, cardiovascular disease, nephropathy and markers of neuropathy
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13 141 that include evidence of foot ulcers, monofilament foot examinations and pulse testing. **Table 1**
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15
16 142 provides an overview of some of the important clinical variables collected from NDR-A and
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19 143 ROSA4.
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22 144 *Statistics Norway (SSB)*: Data gathered from Statistics Norway mainly cover socio-economic
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25 145 factors, including education, disability income, sick-leave and country of birth.
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29 146 *Norwegian Population Register (NPR)*: This register will provide detailed information on
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32 147 migration of the patients within the study, including dates for immigration and/or emigration and
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35 148 death.
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38 149 *Norwegian Prescription Database (NorPD)*: NorPD data represent all dispensed prescriptions by
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41 150 date and ATC-codes for each participant. The OMIT cohort also obtains date of death from
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45 151 NorPD.
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48 152 Further, based on ATC codes we will construct an ATC-code based multi-morbidity score¹³,
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51 153 which will be validated based on its ability to predict 1- and 5-year mortality. The score will then
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1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)

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3 154 serve as an individual measure applicable as either an exposure or an outcome in subsequent
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6 155 research studies.
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9 156 *Norwegian Directorate of Health*. The Norwegian Directorate of Health manages several national
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12 157 registers, including the medical claims register (KUHR) and the Health Personnel Register
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15 158 (HPR), from which we will receive data on GPs and features of their clinical practices. This
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18 159 includes patient list size, waiting list size, patient turnover data and demographics. GP
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21 160 characteristics include specialist status and whether the GP is salaried or self-employed, as well
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24 161 as an overview of the procedure-related payments and diagnoses recorded by the GP, enabling
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27 162 analyses of health economic outcomes.
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32 163 *Patient enrolment and sample size*
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35 164 The eligibility criteria for the OMIT cohort are all T2D patients over 18 years. All patients are
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38 165 identified from the Norwegian Diabetes Register for Adults (NDR-A) or the Rogaland-Oslo-
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41 166 Salten-Akershus-Hordaland (ROSA 4) study, covering the time-period from 2006 to 2019.
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44 167 Subsequently, these data sources are linked to the Norwegian Prescription Database for
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47 168 dispensed medications, the Norwegian Population Register for data on death and migration,
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V5 19/12/2021

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

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

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

178 The NDR-A was established in 2005 with the aim of improving the quality of treatment of people
179 with diabetes in Norway¹⁴. The registry has included outpatient hospital data since 2006,
180 although reporting did not start until 2008. Primary care data has been included since 2009.
181 Since then, the number of included patients in NDR-A has grown steadily. However, mainly due
182 to requirements of written informed consent, enrolment was low in the early years, especially for
183 people with T2D. In response, the ROSA 4 study was created to secure access to representative
184 data on patients with diabetes from diverse clinical settings. ROSA4 is a population-based cross-
185 sectional survey conducted in 2015 (but based on data from the time period 2012-2014) that
186 included 10,248 people with T2D identified by 282 general practitioners (GPs)¹⁵.

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

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3 187 As an extension of the past initiatives, the “Outcomes & Multi-morbidity in Type 2 Diabetes”
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6 188 (OMIT) project has now combined data from the NDR-A and ROSA4. OMIT will carry forward
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9 189 previous research efforts focusing on the quality of care for people with T2D in Norway, although
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13 190 this time with a dedicated focus on high-risk groups often omitted from randomized clinical trials
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16 191 (hence the acronym OMIT).

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19 192 **Figure 2** shows the number of OMIT cohort patients by source and year, as well as patient
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22 193 enrolment over time organized by hospital and primary care sources. **Figure 2** also shows that
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25 194 ROSA4 contributed data in the time-period 2012-2014, although some ROSA4 patients may also
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28 195 have been in the NDR-A prior to and after these years. The ROSA4 study comprises longitudinal
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31 196 laboratory and drug prescription data from 2012-2014 and cross-sectional data on other patient
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34 197 characteristics from 2014. When considering the overlap with the NDR-A, ROSA4 delivered an
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37 198 additional 4,573 patients to the OMIT cohort. Going forward, we expect the cohort to grow
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40 199 further as a more GPs report to the register. Recent changes in national regulations have made
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43 200 it possible for national health registers to apply for inclusion of patients without informed consent
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46 201 if patients have not proactively put forward a request to be excluded¹⁶. In addition, The
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49 202 Norwegian Health Economics Administration (HELFO) has recently introduced a payments to
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52 203 GPs who submit data to the NDR-A. This is likely to accelerate GP reporting further.
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V5 19/12/2021

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

204 Consequently, the OMIT cohort is expected to grow to ~100,000 patients with T2D in 2022

205 (second wave linkages).

206 Between 2006 and 2019, a total of 57,527 individuals have been included in OMIT. Hereof

207 10,242 patients from the ROSA4 study, 42,239 from the NDR-A primary care database and

208 13,876 from the NDR-A hospital database. There is substantial overlap between the databases

209 (**Figure 3**). For the high-risk groups, the current cohort includes data for about 6,500 YOD

210 patients, 15,500 elderly (>75 years), about 9,000 non-western ethnic minority patients, e.g.

211 predominantly South and East Asian or African ethnical background, and 20,500 patients with

212 primary education only.

213 **Figure 4** illustrates development in the national coverage of the cohort via a series of maps,

214 identifying the different counties of Norway. The fill colour indicates the county's total number of

215 registered patients in OMIT, standardized to county population. In 2009, several counties had

216 low coverage, such as the counties Sør-Trøndelag and Telemark, but this has improved over

217 time to all counties having over 100 T2D patients per 100,000 residents included in the OMIT

218 cohort in 2019, and several counties have over 1000 patients per 100,000. Although roughly

219 one-third of GPs reported patients to the NDR-A in 2019, the OMIT-cohort at present only

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

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3 220 includes about 20% of the T2D population in Norway¹⁷. However, all counties are represented,
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6 221 and thus it offers good reliability when studying populations that may differ regionally.
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10 222 *Patient follow-up*

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13 223 The first wave linkages included all data in NDR-A and ROSA4 up until the end of 2019. Patients
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16 224 are generally followed up at least once per year as one annual diabetes control is recommended
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19 225 as the minimum in general practice and GPs now receive a payment per patient for performing
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22 226 annual follow-up and reporting data to the NDR-A. In the current cohort, the median follow-up
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26 227 time between the first and final HbA_{1c} measures is 2 years, with an interquartile range (IQR) of 0
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29 228 to 7 years and maximum of 14 years. The median number of visits is 6 (IQR 1 to 139). Despite
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32 229 having access to data from 2006 to 2009, the median follow-up reflects a large increase in first
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35 230 recordings in NDR-A in 2018 and 2019. To see clinical characteristics of current study
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38 231 participants, please see Table 1 (for more details, please see Chapter "Findings to date").
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41 232 *Future patient enrolment and sample sizes*

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45 233 Going forward, we expect the NDR-A, e.g. the primary source for including patients into OMIT, to
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48 234 include recurring annual data for a growing proportion of the cohort-patients as more GPs are
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51 235 likely to report. Further, the number of recorded measurements per year, especially concerning
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54 236 HbA_{1c}, blood pressure and drug prescriptions, are likely to increase as GPs tend to follow-up
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V5 19/12/2021

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

237 their patients more frequently as compared to the outpatient hospital clinics. As already stated,
238 to increase the sample size of the cohort, we therefore plan to replicate the linkages with new
239 waves of data every three to five years. Thus, we expect the NDR-A to grow, with 15 000 new
240 patients, as observed during 2019, to about 30 000 new patients annually over the next five
241 years. As a result, we expect the OMIT cohort to increase to approximately 100,000 and
242 150,000 patients in 2022 (second wave linkages) and 2025 (third wave linkages), respectively.
243 In addition, already with the second wave, it is planned for the OMIT cohort to be further linked
244 with the Norwegian Patient Registry and the Norwegian Cause of Death Registry. This will
245 further strengthen the comprehensiveness of the cohort and prove solid ground for future studies
246 focusing on mortality related outcomes.

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248 Findings to date

249 In 2019, the average age of the OMIT cohort was 67.4 ± 13.2 years with an average T2D duration
250 of 12.3 ± 8.3 years (Table 1). The mean HbA_{1c} for the whole cohort through the study period was
251 $7.6 \pm 1.5\%$ (59.4 ± 16.3 mmol/mol), BMI was 30.2 ± 5.9 kg/m² and blood pressure $135 \pm 16.1/78 \pm 9.8$
252 mmHg. The prevalence of retinopathy, coronary heart disease and stroke was 10.1%, 21% and
253 6.7%, respectively. Missing data varied greatly depending on the variable, with only 2.5% of the

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

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

256

257 *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.

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V5 19/12/2021

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

259 **Table 1** shows only the main diabetes-related variables by source, and how data from different
260 sources can be mutually supplementary to reduce the impact of missing data obtained from a
261 single source. For example, 14.4% were missing blood pressure measurements from NDR-A
262 hospital records, but due to the higher coverage by the NDR-A primary care records, only 8.2%
263 of the whole cohort have missing blood pressure readings. Even though urinary ACR currently
264 has a high amount of missing data, we will have the advantage of a large sample size in addition
265 to a broad range of other co-variables (including estimates of glomerular filtration rate (eGFR)
266 (calculated by use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)
267 equations using serum creatinine measures¹⁸)) which will allow imputation for missing ACR
268 values.

269 The ROSA4 study, a seminal part of OMIT, has already published many studies related to T2D
270 care in Norway, including findings that non-Western ethnic minorities are diagnosed with T2D at
271 an earlier age than Westerners and are less likely to achieve target HbA_{1c} measures¹⁹. An early
272 study demonstrated modest improvements in diabetes related risk markers from 2005 to 2014 in
273 general practice, including HbA_{1c}, blood pressure and lipids, but revealed suboptimal screening
274 for microvascular complications, such as nephropathy¹⁵. Another ROSA4 study indicated that
275 point-of-care HbA_{1c} testing in general practice was linked to better glycaemic regulation in

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

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3 276 patients with T2D²⁰. Finally, ROSA4 has reported that GP adherence to recommended standard
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6 277 follow-up procedures in T2D was related to both clinic structure and workload²¹.
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10 278 Now that we have expanded the ROSA4 study, we are optimistic the OMIT cohort can further
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13 279 drive the work to enhance our knowledge about how we treat and care for patients with T2D in
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16 280 Norway. This work will position us to put forward concrete and tangible evidence-based
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19 281 recommendations on how diabetes care may be improved, with a special attention to high-risk
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22 282 patients.
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29 284 **Strengths and limitations**

33 285 *Strengths*

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36 286 The OMIT cohort is the first dedicated T2D cohort in Norway constructed from high-quality
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39 287 national registry data that includes patients from all counties, with increasing representativeness
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42 288 over time. Further, OMIT provides separate data from both outpatient clinics and general
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45 289 practices which enables studies of potential differences between these two patient populations.
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49 290 OMIT will support detailed analyses that will generate both nationally generalizable as well as
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52 291 internationally relevant findings. This surpasses the ability of studies such as HUNT and Tromsø
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55 292 Study, both of which are regionally restricted, rely partially on self-reported diabetes diagnoses
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V5 19/12/2021

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

293 and have a lower sample size of patients with T2D²¹. Most OMIT data are longitudinal, which
294 allows us to assess exposures at a time point prior to the defined outcomes. Also, OMIT will
295 provide a basis for studying causes and effects of multi-morbidity rather than only traditional risk
296 factors (e.g. hypertension, hyperglycaemia, hyperlipidaemia etc.). We currently have an
297 extensive dataset that provides a full description of clinical features, socio-demographics,
298 economy and ethnicity, drug prescriptions and drug retrievals, delivered care and treatment
299 processes, and organizational factors including collaborations between primary and specialist
300 care. This provides a strong basis for assessing possible relations between defined exposures
301 and outcomes and to correct for a multitude of confounders. In order to explore potential causal
302 factors, we will draw Directed Acyclic Graphs (DAGs) prior to analyses to identify true
303 confounders to be adjusted for, in line with statistical methods developed to support causal
304 inference in observational data.

305 *Limitations*

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

1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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3 310 stratification or inverse probability weighting. Further, there is risk that GPs willing to participate
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6 311 early on may have provided a higher level of care. This may also introduce bias, which could
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9 312 lower the external validity of primary care NDR-A data, particularly in the earlier years.
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12 313 Therefore, we plan to assess the overall representativeness of the NDR-A primary care data by
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15 314 use of the ROSA4-population, which is considered more representative for Norwegian general
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18 315 practice. Some variables have high levels of missing data, and follow-up time-periods vary
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21 316 between data sources and within patients. Thus, it may also be relevant to perform analysis of
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24 317 potential selection bias due to self-selection and missing data.
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318 **Data Availability Statement**

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

325 **Further details**

326 *Funding*

V5 19/12/2021

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

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3 327 The first phase of linkages was funded by the University of Oslo. Currently, senior researchers
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6 328 and one postdoctoral position (Western Norway University of Applied Sciences (HVL), Norway)
7
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9 329 are funded by their home institutions (for senior researchers: see author affiliation list). The
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13 330 cohort is also funded by The Norwegian Diabetes Association (Diabetesforbundet) and the
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16 331 Norwegian Research Fund for General Practice (Allmenntilleggsforskningsfond), with the
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19 332 latter also funding one PhD-student (University of Oslo (UiO), Norway).
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22 333 *Ethics and ethics approval*

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25 334 The project has obtained ethical approval from Regional Committees for Medical Research
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29 335 Ethics - South East Norway (REC South East (Ref# 74012)) and is approved by the Data
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32 336 Protection Official/Officer at UiO. Data linkage began in mid-2020 for the years 2006-2019. After
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35 337 the final linkages of data from all registers, all researchers are not in any way be able to identify
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38 338 individual patients. We have reduced the number of categories for variables (data minimization)
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41 339 to secure a sufficient number in each cell so that patients cannot be retrospectively identified.
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45 340 Individual researchers will only have access to variables relevant for their research questions,
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48 341 and only after granted approval from REC South East.
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51 342 *Patient and Public Involvement*
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1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)

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3 343 The OMIT-study has received a letter of endorsement from the Norwegian Diabetes Association
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6 344 in addition to financial support, and key senior researchers from the OMIT-study group, including
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9 345 Prof. Emeritus Anne Karen Jenum, over the years with the ROSA4-study have had a long-
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12 346 standing close collaboration with Norwegian Diabetes Association, which we aspire to continue
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16 347 with the OMIT-initiative.
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20 348 To secure that the OMIT project will result in tangible and quantifiable improvements in the
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23 349 clinical care of high-risk patients with T2D, in alignment with patient preferences and identified
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26 350 unmet needs, we have identified the following key strategic objectives and the related target
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29 351 stakeholder and tactics:

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33 352 ***Strategic objective: Strengthen GP diabetes education.***

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37 353 • *Target stakeholder:* Norwegian Medical Association (Den Norske Legeforening (DNLF)) and
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40 354 Association of General Practitioners (*Allmennlegeforeningen*) – later on other Nordic Medical
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43 355 Associations may also be relevant.
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46 356 • *Tactics:* Ensure a dedicated class with focus on high-risk patients is incorporated into the
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50 357 annual pre- and post-gradual national courses in diabetes.
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53 358 ***Strategic objective: Improve clinical guidelines for key high-risk patients.***
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V5 19/12/2021

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

- 359 • *Target stakeholder:* Norwegian guideline author group.
- 360 • *Tactics:* Translate key research findings into concrete suggestions on how to individualize
- 361 guidelines for high-risk patients and on how different drug regimens may help solve key
- 362 clinical issues such as non-adherence, therapeutic inertia and disease control variability in
- 363 high-risk patients.
- 364 ***Strategic objective:* Secure high-risk patients access to innovation (e.g. reimbursement).**
- 365 • *Target stakeholder:* The Norwegian Medicines Agency (Legemiddelverket (LMV)) and the
- 366 Norwegian Directorate of Health (Helsedirektoratet).
- 367 • *Tactics:* Identify and share patient subgroups with most attractive cost-benefit-ratio.
- 368 ***Strategic objective:* Enhance patient competences and empowerment.**
- 369 • *Target stakeholder:* Norwegian Diabetes Association (Diabetes Forbundet).
- 370 • *Tactics:* Norwegian Diabetes Association has written a letter of endorsement and granted
- 371 financial resources to support the OMIT-initiative. Going forward, in close dialogue with the
- 372 Norwegian Diabetes Association, the OMIT-study group will ensure key research findings
- 373 and key takeaways with relevance for patients will be communicated to patients, using both
- 374 the webpage and the membership magazine of Norwegian Diabetes Association.
- 375 ***Strategic objective:* Improve political willingness to invest in high-risk patients.**

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

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

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

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

390
391 With this strategic approach, we aspire that the OMIT-project will help increase public
392 awareness about unmet needs in current care, support patient empowerment by strengthening

V5 19/12/2021

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

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3 393 patient organization competences, influence policy makers to perform relevant and cost-effective
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6 394 investments, improve national guidelines and facilitate that the right patients get access to right
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10 395 treatments at the right time.

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13 396 *Competing interests*

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16
17 397 All authors have filled out and signed a “Disclosure of potential conflicts of interests”-form which
18
19
20 398 can be reproduced upon request. E.S. Buhl is a previous employee of Novo Nordisk (2011-16)
21
22
23 399 and has offered medical consulting and lectures to Novo Nordisk, Sanofi Aventis and
24
25
26
27 400 MundiPharma. J.G. Cooper has received lecturing fees from Novo Nordisk, Sanofi Aventis, Eli
28
29
30 401 Lilly, AstraZeneca, GSK. All other authors declare no conflicts of interests.
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34 402 *Author contributions*

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38 403 Together Dr. E.S. Buhl and Prof. Emeritus A.K. Jenum have initiated and driven the work related
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40
41 404 to drafting the overall OMIT research protocol, to applying for local ethics committee approval
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43
44 405 and to the process of performing the register linkages. Dr. E.S. Buhl is the primary investigator
45
46
47 406 (P.I.) on the OMIT-cohort study and Prof. M. M. Iversen has recently succeeded Prof. Emeritus
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51 407 Dr. A.K. Jenum in the role as Co-P.I.
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1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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3 408 Dr. K. Nøkleby, Dr. T. J. Berg, Prof. T. Iversen, Prof. T Hagen, Dr. J. Cooper, Prof. S. Sandberg
4
5
6 409 and DrMsc. K. F. Løvaas have also provided substantial inputs to the overall OMIT-research
7
8
9 410 protocol. After local ethics committee approval of the study-protocol, Dr. K. R. Richardsen, Prof.
10
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12 411 R. M. Nilsen and Prof. M. M. Iversen have joined the OMIT-study group, and co-P.I. Prof. M. M.
13
14
15 412 Iversen has contributed substantially with the refinement of some of the research questions
16
17
18 413 related to the protocol as well as to the strategic planning of the overall project. The first three
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21 414 Ph.D/Post.Doc.-research projects, out of six planned for the time being, originating from the
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24 415 protocol are in the process of being executed as a 1) PhD.-project focusing on complications in
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27 416 YOD patients (Dr. K. Tibballs based at University of Oslo (UiO) with Dr. E.S. Buhl as supervisor),
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29
30 417 2) as a Post.Doc.-project assessing quality of care in elderly with T2D (Dr. R. B. Strandberg
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33 418 based at Western Norway University of Applied Sciences (HVL) with Prof. M.M. Iversen as
34
35
36 419 supervisor) and 3) a Post.Doc.-project focusing on real-life drug effectiveness in YOD and
37
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39 420 elderly patients with T2D (candidate to be determined).
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41
42 421 Dr. R. B. Forster has worked with the initial analyses and quality check of the data files and has
43
44
45 422 first authored this cohort paper. All other researchers mentioned above each have contributed
46
47
48 423 significantly with the writing and review of this manuscript with last author and P.I. Dr. E. S. Buhl
49
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51 424 taking the role as corresponding author.
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V5 19/12/2021

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

2
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8
9
10 427 work of ROSA4 and NDR-A, as well as the patients and doctors that have contributed data. We
11
12
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16
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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)

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V5 19/12/2021

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

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.

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

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3 Figure 3.

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

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13 NB: When accounting for those overlaps, please note that the first wave cohort has enrolled

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16 57,527 individual patients with type 2 diabetes.
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28 Figure 4.

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32 *Number of registered OMIT patients by year by county, standardised to total county population.*
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36 County legend, e.g. ISO-codes: 1. Østfold; 2 Akershus; 3 Oslo; 4 Hedmark; 5 Oppland; 6

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39 Buskerud; 7 Vestfold; 8 Telemark; 9 Aust-Agder; 10 Vest-Agder; 11 Rogaland; 12 Hordaland;

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42 14 Sogn og Fjordane; 15 Møre og Romsdal; 16 Sør-Trøndelag*; 17 Nord-Trøndelag*; 18 Troms;

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V5 19/12/2021

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

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3 § Regions that contributed to data in the ROSA4 study in 2014: Rogaland, Oslo, Salten - a

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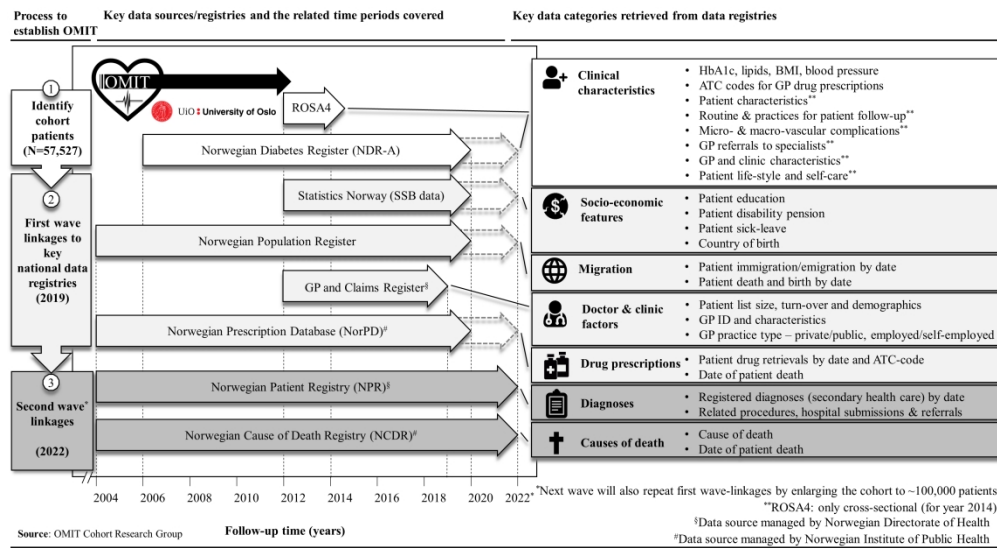


Figure 1. Overview of OMIT cohort construction, covered time-periods and overall data categories and co-variables.

338x190mm (300 x 300 DPI)

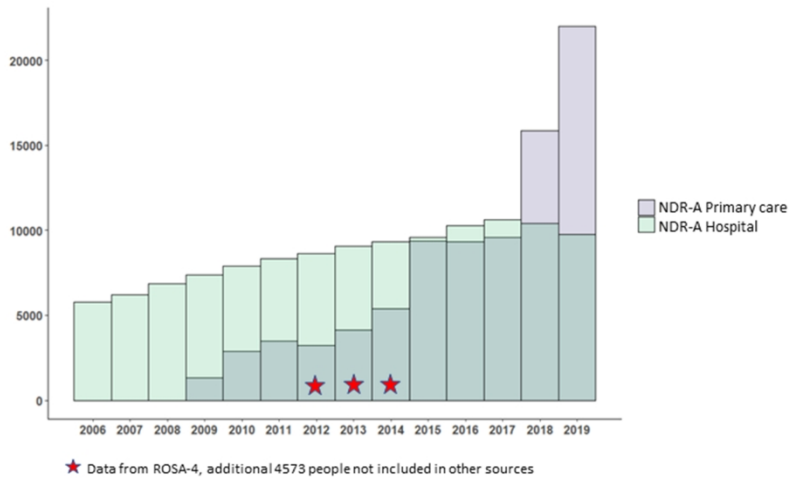


Figure 2.

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.

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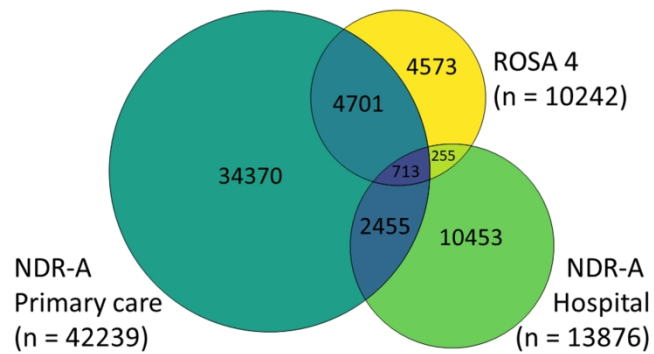


Figure 3.

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.

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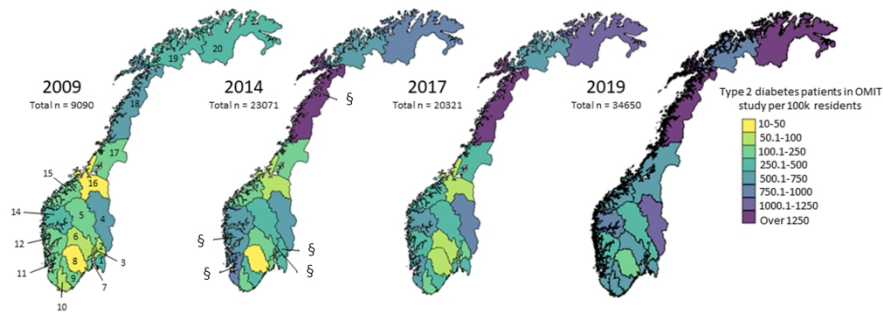


Figure 4.

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.

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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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Secondary Subject Heading:	Epidemiology, General practice / Family practice
Keywords:	DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, PRIMARY CARE, General diabetes < DIABETES & ENDOCRINOLOGY





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

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

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

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12 26 Word count: 4,000 (excl. title page, abstract, tables, acknowledgements, contributions,

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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 $7.6 \pm 1.5\%$

V5 19/12/2021

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

(59.4±16.3 mmol/mol), mean BMI and blood pressure is 30.2±5.9 kg/m² 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.

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

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4 61 • OMIT is expected to grow further and to offer even more exhaustive data via repeated
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7 62 linkages performed every third to fifth year.
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11 63 • OMIT may not be fully representative for Norwegian general practice, especially in the
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14 64 earlier years, as many of the patients then were included from hospital outpatient clinics
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17 65 and are likely to differ from patients cared for only in general practice.
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21 66 • There may be a risk of self-selection bias, especially for the earlier years, as those GPs
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V5 19/12/2021

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

71 Introduction

72 *Background*

73 The prevalence of Type 2 diabetes (T2D) is increasing worldwide, and so is the burden of
74 related vascular complications and death¹. Diabetes is a major cause of cardiovascular disease,
75 blindness², chronic kidney disease³, diabetic foot ulcers⁴ and limb amputations⁵. Beyond the
76 immense reduction in quality of life, these complications lead to reduced labour market
77 participation and inflict a considerable burden on the global economy⁶.

78 Although timely and efficacious interventions can improve outcomes and reduce the economic
79 burden⁷, the evidence for current drug regimens is often limited in patients with greater needs as
80 they are often omitted from clinical trials. Clinical guidelines from the European Association for
81 the Study of Diabetes (EASD)⁸, the American Diabetes Association⁹ and Norwegian Directorate
82 of Health¹⁰ provide guidance on how to manage diabetes treatments and disease control targets
83 based on an individualized approach. However, a key weakness is the guidelines are based on
84 results from trials where only 3.5–35.7% of patients in daily clinical practice would have been
85 eligible to participate¹¹. Therefore, the results from these trials may not be generalizable for the
86 majority of patients, especially vulnerable groups such as 1) those with young onset diabetes
87 (T2D prior to age 40), 2) elderly above 75 years, 3) ethnic minorities, and 4) patients with low

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

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3 88 socio-economic status. Moreover, guidelines provide only a vague guidance as to how diabetes
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10 90 recommendations on how to address a broad range of key barriers to good disease control for
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13 91 vulnerable groups¹². Consequently, we need more evidence to better understand the current
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16 92 unmet needs and evidence documenting the effectiveness, cost-effectiveness and safety of
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19 93 various treatments and clinical procedures in relation to how they may impact both disease
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22 94 control and harder disease outcomes in high-risk patients. As high-risk patients have proven
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25 95 difficult to include in prospective interventional trials, instead we see a great opportunity to
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28 96 employ non-interventional, observational data already present in various high-quality national
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35 98 The “Outcomes & Multi-morbidity in Type 2 Diabetes” (OMIT) cohort, which is based on multiple
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38 99 linkages between various Norwegian population-based registries, was established to support
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41 100 non-interventional observational studies of high-risk patients with T2D treated in general
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44 101 practice, in outpatient hospital clinics, or by shared care. The first wave of the OMIT cohort focus
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47 102 primarily on the following key high-risk groups: (1) young onset diabetes (YOD - T2D prior to age
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50 103 40), (2) elderly patients (>75 years of age), (3) non-western ethnic minorities (i.e. non-western
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53 104 immigrants excluding Eastern European immigrants), and (4) low socio-economic status (SES)

V5 19/12/2021

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

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

109 *OMIT research questions*

110 Currently, we have three broad research questions:

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

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

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

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

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

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

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134 Cohort description

135 *Data sources and categories*

V5 19/12/2021

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

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

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

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

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

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

2
3 152 Further, based on ATC codes we will construct an ATC-code based multi-morbidity score¹³,
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6 153 which will be validated based on its ability to predict 1- and 5-year mortality. The score will then
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9
10 154 serve as an individual measure applicable as either an exposure or an outcome in subsequent
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12
13 155 research studies.

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15
16 156 *Norwegian Directorate of Health*. The Norwegian Directorate of Health manages several national
17
18
19 157 registers, including the medical claims register (KUHR) and the Health Personnel Register
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21
22 158 (HPR), from which we will receive data on GPs and features of their clinical practices. This
23
24
25 159 includes patient list size, waiting list size, patient turnover data and demographics. GP
26
27
28 160 characteristics include specialist status and whether the GP is salaried or self-employed, as well
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30
31 161 as an overview of the procedure-related payments and diagnoses recorded by the GP, enabling
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34 162 analyses of health economic outcomes.

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38 163 *Patient enrolment and sample size*

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41 164 The eligibility criteria for the OMIT cohort are all T2D patients over 18 years. All patients are
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43
44 165 identified from the Norwegian Diabetes Register for Adults (NDR-A) or the Rogaland-Oslo-
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46
47 166 Salten-Akershus-Hordaland (ROSA 4) study, covering the time-period from 2006 to 2019.
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50 167 Subsequently, these data sources are linked to the Norwegian Prescription Database for
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53 168 dispensed medications, the Norwegian Population Register for data on death and migration,
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V5 19/12/2021

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

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3 169 Statistics Norway for data on socio-economic factors and ethnicity and the Norwegian

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6 170 Directorate of Health for data on the general practices and clinical procedures involved in the

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8
9 171 care of cohort patients.

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11
12 172 **Figure 2** shows the different cohort-data sources, the time-periods covered with the first and

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15 173 second wave register linkages and the different data categories made available for the included

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17
18 174 cohort patients. For more details, please see chapter “Data sources and categories” below. First

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21 175 wave linkages involves data until December 31st 2019 whereas second wave linkages will

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24 176 extend covered time period until December 31st 2022 and supplement the cohort with additional

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26
27 177 data from the Norwegian Patient Registry and Norwegian Cause of Death Registry.

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29
30 178 The NDR-A was established in 2005 with the aim of improving the quality of treatment of people

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32
33 179 with diabetes in Norway¹⁴. The registry has included outpatient hospital data since 2006,

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35
36 180 although reporting did not start until 2008. Primary care data has been included since 2009.

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39 181 Since then, the number of included patients in NDR-A has grown steadily. However, mainly due

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41
42 182 to requirements of written informed consent, enrolment was low in the early years, especially for

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45 183 people with T2D. In response, the ROSA 4 study was created to secure access to representative

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48 184 data on patients with diabetes from diverse clinical settings. ROSA4 is a population-based cross-

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

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3 185 sectional survey conducted in 2015 (but based on data from the time period 2012-2014) that

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5
6 186 included 10,248 people with T2D identified by 282 general practitioners (GPs) ¹⁵.

7
8
9 187 As an extension of the past initiatives, the “Outcomes & Multi-morbidity in Type 2 Diabetes”

10
11
12 188 (OMIT) project has now combined data from the NDR-A and ROSA4. OMIT will carry forward

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14
15 189 previous research efforts focusing on the quality of care for people with T2D in Norway, although

16
17
18 190 this time with a dedicated focus on high-risk groups often omitted from randomized clinical trials

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20
21 191 (hence the acronym OMIT).

22
23
24 192 **Figure 3** shows the number of OMIT cohort patients by source and year, as well as patient

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26
27 193 enrolment over time organized by hospital and primary care sources. **Figure 3** also shows that

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29
30 194 ROSA4 contributed data in the time-period 2012-2014, although some ROSA4 patients may also

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32
33 195 have been in the NDR-A prior to and after these years. The ROSA4 study comprises longitudinal

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35
36 196 laboratory and drug prescription data from 2012-2014 and cross-sectional data on other patient

37
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39 197 characteristics from 2014. When considering the overlap with the NDR-A, ROSA4 delivered an

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41
42 198 additional 4,573 patients to the OMIT cohort. Going forward, we expect the cohort to grow

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44
45 199 further as a more GPs report to the register. Recent changes in national regulations have made

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47
48 200 it possible for national health registers to apply for inclusion of patients without informed consent

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50
51 201 if patients have not proactively put forward a request to be excluded¹⁶. In addition, The

V5 19/12/2021

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

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3 202 Norwegian Health Economics Administration (HELFO) has recently introduced a payments to

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6 203 GPs who submit data to the NDR-A. This is likely to accelerate GP reporting further.

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8
9 204 Consequently, the OMIT cohort is expected to grow to ~100,000 patients with T2D in 2022

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12 205 (second wave linkages).

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14
15 206 Between 2006 and 2019, a total of 57,527 individuals have been included in OMIT. Hereof

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17
18 207 10,242 patients from the ROSA4 study, 42,239 from the NDR-A primary care database and

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20
21 208 13,876 from the NDR-A hospital database. There is substantial overlap between the databases

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23
24 209 (**Figure 4**). For the high-risk groups, the current cohort includes data for about 6,500 YOD

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26
27 210 patients, 15,500 elderly (>75 years), about 9,000 non-western ethnic minority patients, e.g.

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29
30 211 predominantly South and East Asian or African ethnical background, and 20,500 patients with

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33 212 primary education only.

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36 213 **Figure 5** illustrates development in the national coverage of the cohort via a series of maps,

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38
39 214 identifying the different counties of Norway. The fill colour indicates the county's total number of

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41
42 215 registered patients in OMIT, standardized to county population. In 2009, several counties had

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44
45 216 low coverage, such as the counties Sør-Trøndelag and Telemark, but this has improved over

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48 217 time to all counties having over 100 T2D patients per 100,000 residents included in the OMIT

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51 218 cohort in 2019, and several counties have over 1000 patients per 100,000. Although roughly

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

2
3 219 one-third of GPs reported patients to the NDR-A in 2019, the OMIT-cohort at present only

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5
6 220 includes about 20% of the T2D population in Norway¹⁷. However, all counties are represented,

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8
9 221 and thus it offers good reliability when studying populations that may differ regionally.

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12
13 222 *Patient follow-up*

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16 223 The first wave linkages included all data in NDR-A and ROSA4 up until the end of 2019. Patients

17
18
19 224 are generally followed up at least once per year as one annual diabetes control is recommended

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21
22 225 as the minimum in general practice and GPs now receive a payment per patient for performing

23
24
25 226 annual follow-up and reporting data to the NDR-A. In the current cohort, the median follow-up

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28 227 time between the first and final HbA_{1c} measures is 2 years, with an interquartile range (IQR) of 0

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30
31 228 to 7 years and maximum of 14 years. The median number of visits is 6 (IQR 1 to 139). Despite

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33
34 229 having access to data from 2006 to 2009, the median follow-up reflects a large increase in first

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36
37 230 recordings in NDR-A in 2018 and 2019. To see clinical characteristics of current study

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40 231 participants, please see Table 1 (for more details, please see Chapter "Findings to date").

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44 232 *Future patient enrolment and sample sizes*

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47 233 Going forward, we expect the NDR-A, e.g. the primary source for including patients into OMIT, to

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49
50 234 include recurring annual data for a growing proportion of the cohort-patients as more GPs are

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52
53 235 likely to report. Further, the number of recorded measurements per year, especially concerning

V5 19/12/2021

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

236 HbA_{1c}, blood pressure and drug prescriptions, are likely to increase as GPs tend to follow-up
237 their patients more frequently as compared to the outpatient hospital clinics. As already stated,
238 to increase the sample size of the cohort, we therefore plan to replicate the linkages with new
239 waves of data every three to five years. Thus, we expect the NDR-A to grow, with 15 000 new
240 patients, as observed during 2019, to about 30 000 new patients annually over the next five
241 years. As a result, we expect the OMIT cohort to increase to approximately 100,000 and
242 150,000 patients in 2022 (second wave linkages) and 2025 (third wave linkages), respectively.
243 In addition, already with the second wave, it is planned for the OMIT cohort to be further linked
244 with the Norwegian Patient Registry and the Norwegian Cause of Death Registry. This will
245 further strengthen the comprehensiveness of the cohort and prove solid ground for future studies
246 focusing on mortality related outcomes.

247

248 Findings to date

249 In 2019, the average age of the OMIT cohort was 67.4±13.2 years with an average T2D duration
250 of 12.3±8.3 years (**Table 1**). The mean HbA_{1c} for the whole cohort through the study period was
251 7.6±1.5% (59.4±16.3 mmol/mol), BMI was 30.2±5.9 kg/m² and blood pressure 135±16.1/78±9.8
252 mmHg. The prevalence of retinopathy, coronary heart disease and stroke was 10.1%, 21% and

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

253 6.7%, respectively. Missing data varied greatly depending on the variable, with only 2.5% of the
 254 cohort missing HbA_{1c} measures, while up to 52.6% were missing urinary albumin creatinine ratio
 255 (ACR).

256

257 *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.

V5 19/12/2021

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

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.

258

259 **Table 1** shows only the main diabetes-related variables by source, and how data from different
260 sources can be mutually supplementary to reduce the impact of missing data obtained from a
261 single source. For example, 14.4% were missing blood pressure measurements from NDR-A
262 hospital records, but due to the higher coverage by the NDR-A primary care records, only 8.2%
263 of the whole cohort have missing blood pressure readings. Even though urinary ACR currently
264 has a high amount of missing data, we will have the advantage of a large sample size in addition
265 to a broad range of other co-variables (including estimates of glomerular filtration rate (eGFR)
266 (calculated by use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)
267 equations using serum creatinine measures¹⁸)) which will allow imputation for missing ACR
268 values.

269 The ROSA4 study, a seminal part of OMIT, has already published many studies related to T2D
270 care in Norway, including findings that non-Western ethnic minorities are diagnosed with T2D at
271 an earlier age than Westerners and are less likely to achieve target HbA_{1c} measures¹⁹. An early
272 study demonstrated modest improvements in diabetes related risk markers from 2005 to 2014 in
273 general practice, including HbA_{1c}, blood pressure and lipids, but revealed suboptimal screening
274 for microvascular complications, such as nephropathy¹⁵. Another ROSA4 study indicated that

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

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3 275 point-of-care HbA_{1c} testing in general practice was linked to better glycaemic regulation in
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6 276 patients with T2D²⁰. Finally, ROSA4 has reported that GP adherence to recommended standard
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9 277 follow-up procedures in T2D was related to both clinic structure and workload²¹.

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13 278 Now that we have expanded the ROSA4 study, we are optimistic the OMIT cohort can further
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16 279 drive the work to enhance our knowledge about how we treat and care for patients with T2D in
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19 280 Norway. This work will position us to put forward concrete and tangible evidence-based
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22 281 recommendations on how diabetes care may be improved, with a special attention to high-risk
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25
26 282 patients.

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30 31 32 284 **Strengths and limitations**

33 34 35 36 285 *Strengths*

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39 286 The OMIT cohort is the first dedicated T2D cohort in Norway constructed from high-quality
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42 287 national registry data that includes patients from all counties, with increasing representativeness
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46 288 over time. Further, OMIT provides separate data from both outpatient clinics and general
47
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49 289 practices which enables studies of potential differences between these two patient populations.
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52 290 OMIT will support detailed analyses that will generate both nationally generalizable as well as
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55 291 internationally relevant findings. This surpasses the ability of studies such as HUNT and Tromsø

V5 19/12/2021

1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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3 292 Study, both of which are regionally restricted, rely partially on self-reported diabetes diagnoses
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6 293 and have a lower sample size of patients with T2D²¹. Most OMIT data are longitudinal, which
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8
9 294 allows us to assess exposures at a time point prior to the defined outcomes. Also, OMIT will
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12 295 provide a basis for studying causes and effects of multi-morbidity rather than only traditional risk
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15 296 factors (e.g. hypertension, hyperglycaemia, hyperlipidaemia etc.). We currently have an
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17
18 297 extensive dataset that provides a full description of clinical features, socio-demographics,
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20
21 298 economy and ethnicity, drug prescriptions and drug retrievals, delivered care and treatment
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24 299 processes, and organizational factors including collaborations between primary and specialist
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27 300 care. This provides a strong basis for assessing possible relations between defined exposures
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29
30 301 and outcomes and to correct for a multitude of confounders. In order to explore potential causal
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33 302 factors, we will draw Directed Acyclic Graphs (DAGs) prior to analyses to identify true
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35
36 303 confounders to be adjusted for, in line with statistical methods developed to support causal
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39 304 inference in observational data.
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43 305 *Limitations*

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45 306 In this first wave of linkages, a substantial proportion of patients in the cohort are included from
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48 307 hospital outpatient clinics, which are likely to differ from patients cared for only in general
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51 308 practice, a condition reflected by a mean HbA_{1c} for the whole cohort as high as 7.6% (59.4±16.3
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1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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3 309 mmol/mol). Thus, sampling bias may be present and may require post-hoc corrections such as
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6 310 stratification or inverse probability weighting. Further, there is risk that GPs willing to participate
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8
9 311 early on may have provided a higher level of care. This may also introduce bias, which could
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12 312 lower the external validity of primary care NDR-A data, particularly in the earlier years.
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16 313 Therefore, we plan to assess the overall representativeness of the NDR-A primary care data by
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18
19 314 use of the ROSA4-population, which is considered more representative for Norwegian general
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22 315 practice. Some variables have high levels of missing data, and follow-up time-periods vary
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25 316 between data sources and within patients. Thus, it may also be relevant to perform analysis of
26
27
28 317 potential selection bias due to self-selection and missing data.
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31 318 **Data Availability Statement**

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36 319 All OMIT data are stored and analysed on the platform for safe storage of sensitive data (TSD)
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38
39 320 at the University of Oslo until 2035. In support of collaborative research projects, access can be
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41
42 321 granted after approval by the OMIT-study group, the Regional Committee for Medical and Health
43
44
45 322 Research Ethics and the data owner at the University of Oslo. Project requests can be directed
46
47
48 323 to Esben Selmer Buhl at the Department of General Practice, Institute of Health and Society,
49
50
51 324 University of Oslo (email: e.s.buhl@medisin.uio.no)
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V5 19/12/2021

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

325 **Further details**

326 *Funding*

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

333 *Ethics and ethics approval*

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

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

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3 342 *Patient and Public Involvement*

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6 343 The OMIT-study has received a letter of endorsement from the Norwegian Diabetes Association
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10 344 in addition to financial support, and key senior researchers from the OMIT-study group, including
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12
13 345 Prof. Emeritus Anne Karen Jenum, over the years with the ROSA4-study have had a long-
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16 346 standing close collaboration with Norwegian Diabetes Association, which we aspire to continue
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18
19 347 with the OMIT-initiative.

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23 348 To secure that the OMIT project will result in tangible and quantifiable improvements in the
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25
26 349 clinical care of high-risk patients with T2D, in alignment with patient preferences and identified
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29 350 unmet needs, we have identified the following key strategic objectives and the related target
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32
33 351 stakeholder and tactics:

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35
36 352 *Strategic objective: Strengthen GP diabetes education.*

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40 353 • *Target stakeholder:* Norwegian Medical Association (Den Norske Legeforening (DNLFF)) and
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42
43 354 Association of General Practitioners (*Allmennlegeforeningen*) – later on other Nordic Medical
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45
46 355 Associations may also be relevant.
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50 356 • *Tactics:* Ensure a dedicated class with focus on high-risk patients is incorporated into the
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53 357 annual pre- and post-gradual national courses in diabetes.
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V5 19/12/2021

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

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

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

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

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

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

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

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

2
3 373 and key takeaways with relevance for patients will be communicated to patients, using both

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5
6 374 the webpage and the membership magazine of Norwegian Diabetes Association.

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8
9
10 375 ***Strategic objective: Improve political willingness to invest in high-risk patients.***

11
12
13 376 • *Target stakeholders:* Public media, Ministry of Health and Care Services and other political
14
15
16 377 key decision makers.

17
18
19
20 378 • *Tactics:* Disseminate data and key takeaways related to current unmet needs in diabetes

21
22
23 379 care but also communicate key conclusions regarding the effectiveness and cost-

24
25
26 380 effectiveness of various treatments and interventions to build public and political awareness

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28
29 381 of inequality in diabetes outcomes and use evidence to shift focus from short-term budget

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31
32 382 impact to impact in the long-term on compiled disease life-cycle costs.

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36 383 ***Strategic objective: Ensure generated hypotheses are tested in prospective interventional***

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38
39 384 ***studies.***

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41
42
43 385 • *Target stakeholders:* Diabetes researchers in Norway and abroad and researchers involved

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46 386 in Norwegian general practice research network.

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49 387 • *Tactics:* Ensure scientific data are presented at national and international scientific

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52 388 conferences and published in high-impact peer reviewed journals. In addition, identify

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55 389 hypotheses relevant to test in future prospective and interventional studies.

V5 19/12/2021

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

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

396 *Competing interests*

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

402 *Author contributions*

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

1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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4 406 (P.I.) on the OMIT-cohort study and Prof. M. M. Iversen has recently succeeded Prof. Emeritus
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6
7 407 Dr. A.K. Jenum in the role as Co-P.I.
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10 408 Dr. K. Nøkleby, Dr. T. J. Berg, Prof. T. Iversen, Prof. T Hagen, Dr. J. Cooper, Prof. S. Sandberg
11
12
13 409 and DrMsc. K. F. Løvaas have also provided substantial inputs to the overall OMIT-research
14
15
16 410 protocol. After local ethics committee approval of the study-protocol, Dr. K. R. Richardsen, Prof.
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18
19 411 R. M. Nilsen and Prof. M. M. Iversen have joined the OMIT-study group, and co-P.I. Prof. M. M.
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21
22 412 Iversen has contributed substantially with the refinement of some of the research questions
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24
25 413 related to the protocol as well as to the strategic planning of the overall project. The first three
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28 414 Ph.D/Post.Doc.-research projects, out of six planned for the time being, originating from the
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32 415 protocol are in the process of being executed as a 1) PhD.-project focusing on complications in
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35 416 YOD patients (Dr. K. Tibballs based at University of Oslo (UiO) with Dr. E.S. Buhl as supervisor),
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38 417 2) as a Post.Doc.-project assessing quality of care in elderly with T2D (Dr. R. B. Strandberg
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41 418 based at Western Norway University of Applied Sciences (HVL) with Prof. M.M. Iversen as
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44 419 supervisor) and 3) a Post.Doc.-project focusing on real-life drug effectiveness in YOD and
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47 420 elderly patients with T2D (candidate to be determined).
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51 421 Dr. R. B. Forster has worked with the initial analyses and quality check of the data files and has
52
53
54 422 first authored this cohort paper. All other researchers mentioned above each have contributed
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V5 19/12/2021

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

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3 423 significantly with the writing and review of this manuscript with last author and P.I. Dr. E. S. Buhl

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6 424 taking the role as corresponding author.

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16 427 work of ROSA4 and NDR-A, as well as the patients and doctors that have contributed data. We

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19 428 thank the Norwegian Diabetes Association (Diabetesforbundet) and for the Lillian and Werner

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22 429 Næss Scholarship and research fund for supporting authors associated with OMIT.

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V5 19/12/2021

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

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3 Figure legends

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6 Figure 1.

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

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33 *Overview of OMIT cohort construction, covered time-periods and overall data categories and*
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35 *co-variables.*
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41 Figure 3.

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45 *Number of OMIT cohort patients by source and year (first wave linkages).*
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50 The bars shown above only indicate the number of OMIT-patients reported to the NDR-A
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52 registry. Although reporting to the NDR-A registry did not start until 2008, please note that the
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1 Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT)
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3 current cohort still includes some outpatient hospital data for the years 2006-2007. The green
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6 and transparent bars, placed in a front position, reflect the number of patients by year reported
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9 to NDR-A by hospital clinics, whereas violet bars, placed behind the green transparent bars,
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12 give the number of patients reported by year to the NDR-A by GPs. For the years 2012-14,
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15 please note that the ROSA4-data base contributed with additional 4,573 GP patients to the
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18 cohort which, however, are not accounted for in the shown violet bars.
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27 Figure 4.

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29 *Venn diagram of overlap for total number of registered patients in OMIT cohort, with the first*
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32 *wave linkages, from the three different sources.*
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37 NB: When accounting for those overlaps, please note that the first wave cohort has enrolled
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40 57,527 individual patients with type 2 diabetes.
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51 Figure 5.

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55 *Number of registered OMIT patients by year by county, standardised to total county population.*
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V5 19/12/2021

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

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3 County legend, e.g. ISO-codes: 1. Østfold; 2 Akershus; 3 Oslo; 4 Hedmark; 5 Oppland; 6

7 Buskerud; 7 Vestfold; 8 Telemark; 9 Aust-Agder; 10 Vest-Agder; 11 Rogaland; 12 Hordaland;

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10 14 Sogn og Fjordane; 15 Møre og Romsdal; 16 Sør-Trøndelag*; 17 Nord-Trøndelag*; 18 Troms;

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13 20 Finnmark.

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

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21 § Regions that contributed to data in the ROSA4 study in 2014: Rogaland, Oslo, Salten - a

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23
24 region in Nordland - , Akershus and Hordaland.

Projects		1. Burden of multi-morbidity			2. Real-life drug utilization & performance			3. Variability in disease control (quality of care)					
		All patients Validation of ATC MM-index*	YOD patients	Elderly** patients	Minority & low SES patients	YOD patients	Elderly patients	Minority & low SES patients	Organisation & processes of care	YOD patients	Elderly patients	Minority & low SES patients	
<input type="checkbox"/> Validation study <input type="checkbox"/> Two Post.doc./Ph.D. projects <input type="checkbox"/> Two Post.doc./Ph.D. projects <input type="checkbox"/> Tor Iversen project <input type="checkbox"/> Two Post.doc./Ph.D. project	Sub-projects/ Key risk groups												
	Key exposures (E) and/or covariates (C)	<ul style="list-style-type: none"> Diabetes complications Yong-onset diabetes (YOD)[†] Patient lifestyle & self-care Variability in disease control GP prescription pattern Patient drug retrievals by ATC-code Coordination & level of care Elderly^{**} Clinic characteristics/practice type Organization and processes of care Multi-Morbidity Patient ethnicity & socio-economy Patient characteristics Patient migration/emigration GP characteristics Disability pension & sick-leave Patient drug adherence Co-morbidity by category Poly-pharmacy Adverse drug interactions 	C ¹ , C ² , C ³ E ¹ , E ² , E ³ C ¹ , C ² , C ³	C ² C ¹ , C ²	C ¹ , C ² C ¹ , C ²	C ¹ , C ² C ¹ , C ²	C ¹ , C ² , C ³ C ¹ , C ²	C ¹ C ¹ , C ²	E ₁ , S ₁ E ₂ , S ₂ E ₃ , S ₃ C ¹ , C ² , C ³ C ¹ , C ²	C ² E ¹ , E ² , E ³ C ¹ , C ² , C ³ E ₁	C ² C ¹ , C ² E ¹	C ² C ¹ , C ² E ¹	
Key outcomes	<ul style="list-style-type: none"> Variability in disease control Yong-onset diabetes (YOD)[†] Diabetes-specific complications Disability & sick-leave Real-life drug or cost-effectiveness Multi-morbidity Drug treatment cascade Mortality/survival Patient drug adherence Co-morbidity by category Polypharmacy Adverse drug interactions 	S ¹	P ¹ S ¹ , S ² P ²	S ¹ , S ²	S ² S ¹ , S ² P ²	P ² S ² P ¹	P ¹	S ¹ S ¹ , S ²	S ¹ , S ²	P ¹ , S ¹ P ¹ , P ²	P ² S ¹	P ¹ S ¹	P ² S ¹
~20-24 research papers	Number of paper(s)	1	3	1-2	1-2	2	3	2	2	3	1-2	1-2	

Source: OMIT Study Group *ATCMM Index = ATC-based Multi-Morbidity Index; P = Primary Outcome; S = Secondary Outcome; ¹=Paper 1, ²= Paper 2, ³=Paper 3; [†]Age and gender only; ^{**}Age at diabetes onset ≤40 years; ^{**}Age only (≥75 years)

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.

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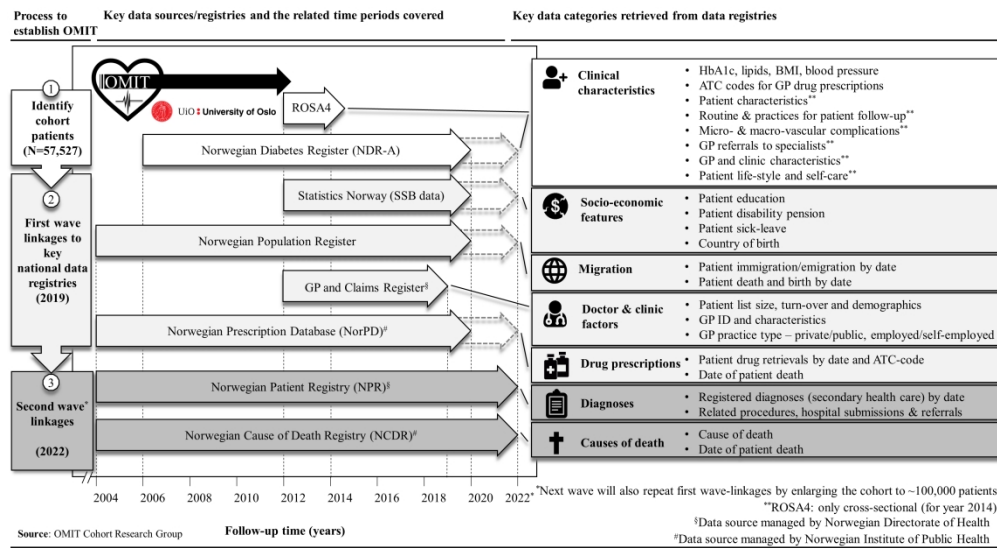


Figure 2. Overview of OMIT cohort construction, covered time-periods and overall data categories and co-variables.

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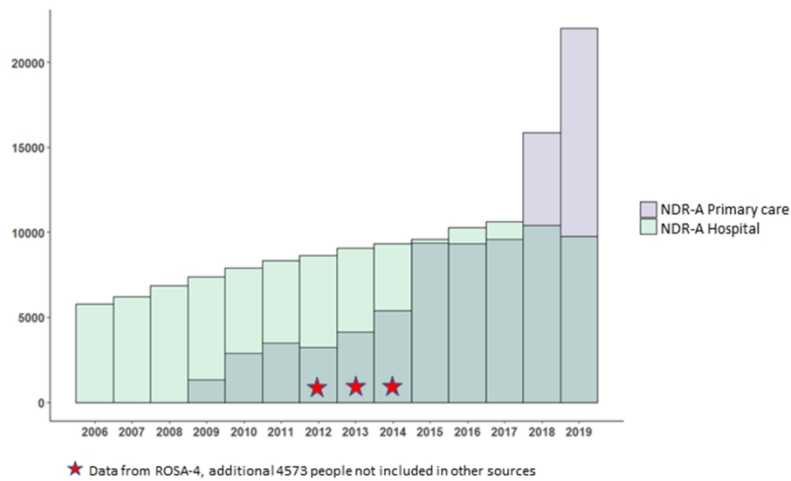


Figure 3.

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.

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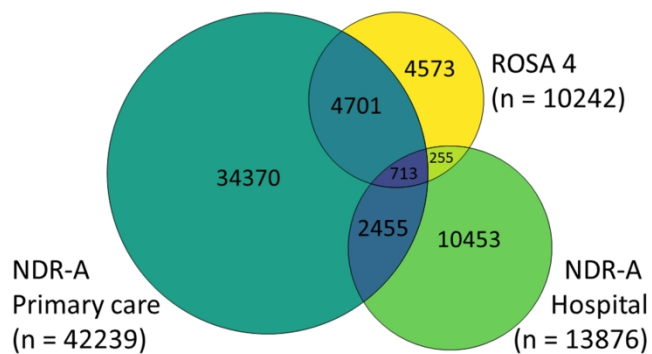


Figure 4.

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.

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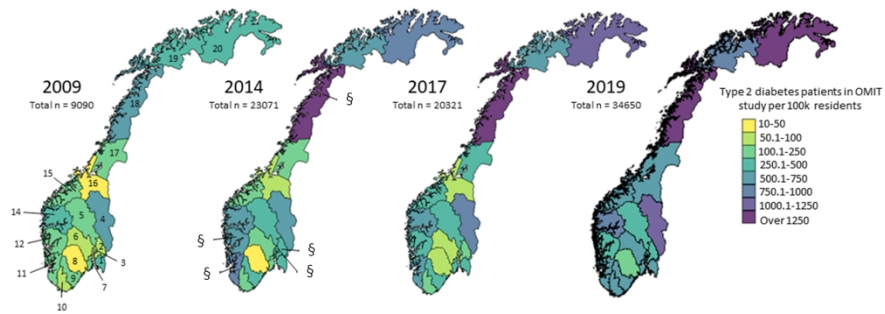


Figure 5.

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.
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