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LISTEN TO YOUR DOCTOR, OR ELSE!: MEDICATION UNDER-USE AND OVERUSE AND LONG-TERM HEALTH OUTCOMES OF DANISH DIABETES PATIENTS

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ABSTRACT

We use Danish diabetes registry and health insurance data to analyze the extent, consequences, and determinants of under-use and overuse of oral anti-diabetic drugs.

Less than half of patients consume the appropriate amount of medication--between 90% and 110% of the amount prescribed by their doctors.

The life expectancy of patients consuming the appropriate amount is 2.5 years greater than that of patients consuming less than 70% of the prescribed amount, and 3.2 years greater than that of patients consuming more than 130% of the prescribed amount, controlling for time since diagnosis, insulin dependence, comorbidities, age, gender and education. Patients consuming the appropriate amount are also less likely to be hospitalized than under- or over-users.

Pharmaceutical innovation appears to have reduced medication under-use and overuse: patients using newer drugs are significantly more likely to consume the appropriate amount, controlling for socioeconomic factors, average number of pills and average daily out-of-pocket costs.

Defined Daily Doses published by the World Health Organization substantially overstate the appropriate level of consumption of these medications.

Patients who don't adhere to recommended medication regimens may also disregard other physician instructions. Medication under-use and overuse could easily be monitored to identify patients at risk and enact interventions.

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1. Introduction

Medication non-adherence is regarded as one of the main factors that reduce the effectiveness of drug therapies in clinical practice as compared to the expected effect from clinical trials. For many diseases including diabetes, medication non-adherence has been shown to be associated with long-term complications, hospitalizations, premature mortality, and billions of dollars per year in avoidable direct health care costs (1-5). It is therefore an area of concern to health professionals, insurers, policy makers, and researchers alike.

Adherence is the extent to which the patient's behavior (medication-taking and lifestyle practices) coincides with medical or health advice (6). Even though a great deal of prior research has been done in the area, there is no gold standard for identifying identify non-adherence. Many studies have used a cut-off point of ≤80% of the targeted adherence level to classify patients as non-adherent patients across various diseases (4; 7; 8). However, ideally the adherence measure should take the specific epidemiology of the disease adequately into account and may therefore be disease- and even context-specific, depending on the quality of the available data.

In health policy making there is an increasing desire to use administratively collected data, such as claims or registry data, as a controlling tool in order to monitor quality of care for example to design disease management programs (DMPs) in a more effective way. In order to be a useful tool for quality management, a meaningful indicator of patient adherence should be a good predictor of health outcomes. It should be easy to collect, and should be available in a timely manner to provide feedback to health professionals.

The current study adds to the existing literature on adherence by introducing and validating a new measure of drug adherence in order to assess whether pharmaceutical claims data provide a valuable source to monitor patient adherence to oral anti-diabetic drugs (OADs) to be used in quality management programs. We assess the level of non-adherence in the Danish population for different OADs using several measures of medication adherence and stress the importance of using actually prescribed dosages instead of standard drug-specific defined daily dosages (DDDs) as defined by the WHO Center for Drug Statistics (9). Our preferred measure for assessing adherence is based on deviations from the prescribed dosage, and we demonstrate the usefulness of this measure in the context of diabetes care by estimating the impact of adherence on long-term health outcomes, such as hospitalizations, mortality rates, and life expectancy. Our measure is better suited to the context of diabetes, as it takes the specific epidemiology of the disease - which is usually characterized by

decreasing sensitivity to drugs necessitating higher dosages over time - better into account[1] (10). Moreover, it recognizes that drug therapy is only one dimension of diabetes treatment, and that non-adherence may not only be driven by financial constraints but that other psycho-social factors may prevent patients from following treatment recommendations. It is better able to deal with overconsumption of OADs, a phenomenon that has been observed previously, but which has been largely neglected in previous adherence research (11). Finally, we explore which factors are associated with good treatment adherence in order to make policy recommendations on how to improve adherence to OAD therapy.

Most existing adherence studies focus on short-term (surrogate) health outcomes, such as average blood glucose levels (HbA1c) or specific complications, or they do not assess health outcomes at all (8; 12-16). Some papers examine the effect of drug adherence on health care utilization such as hospitalizations (2; 13), and a few papers examine the effect of adherence on long-term health outcomes such as mortality (17; 18). We are not aware that any studies have investigated the impact of adherence on life expectancy in a diabetes population yet, as this requires long follow-up. While mortality and life expectancy are closely related, life expectancy is a more useful measure, as for example cost-effectiveness analysis is based on the number of (quality-adjusted) life years gained.[2]

Assuming that pharmaceutical treatment is effective, our basic hypothesis is that negative health outcomes are a function of non-adherence and that this is best measured as deviations from prescribed dosages. We first estimate the impact of adherence on hospitalizations and mortality. We do this for two reasons. First, to demonstrate the comparability of our approach with previous analyses that have investigated the association of adherence and health outcome measures, such as hospitalizations or mortality. And second, because health insurers are often interested in whether health interventions, in addition to improving patients' health, have the potential to reduce health care costs. As hospitalizations are not only a measure of intermediate health outcomes, but are typically also very costly, hospitalizations may be a proxy for medical costs. Subsequently, we turn to the gold standard for assessing effectiveness of health interventions and estimate the impact on longevity in order to demonstrate the benefit of measuring and monitoring adherence according to deviations from prescribed dosages. We find that patients who deviate from the prescribed dosage by more than 10% already have a significantly lower life expectancy than patients who follow their drug treatment schedule more closely. Patients who consume less than 90% or more than 110% of the prescribed

[1] See instruction leaflet metformin, glibenclamid or combinations
[2] The terms longevity and life expectancy are used interchangeably in this paper.

dosage are also significantly more likely to be hospitalized than patients who follow the prescribed regimen most closely. Finally, patients tend to be more adherent to newer drugs: Patients who take OADs launched after 1995 have a 13.3% higher probability of deviating less than 10% from the prescribed dosage than patients taking older drugs.

The rest of the paper proceeds as follows: Section 2 provides some background on diabetes and its treatment essential for understanding the construction of our adherence measure. Section 3 explains study design and methodology. Section 4 presents the results and section 5 discusses the results in light of the previous literature and policy implications.

2. Background on diabetes

Diabetes is a chronic metabolic disease, which occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. This results in increased concentration of glucose in the blood (hyperglycemia), which over time leads to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. The most common form is type 2 diabetes, which accounts for about 85% of diabetes cases and usually occurs in adults. It often results from excess body weight and physical inactivity. In the past three decades the prevalence of type 2 diabetes has risen drastically in countries of all income levels. According to WHO estimates, about 9% of the adult population worldwide has type 2 diabetes (19). Most type 2 diabetes patients are above the age of 50 and comorbidities are very common.

Type 2 diabetes is managed by a 'step-up regimen'. This usually starts with diet and exercise, followed by the addition of oral blood-glucose lowering drugs. If good metabolic control is not maintained otherwise, patients are finally transferred to insulin (20). The insulin sensitivity of most patients with type 2 diabetes decreases gradually over time, so that treatment with oral anti-diabetic drugs (OADs) usually starts with a low dosage and is slowly increased to the maximum tolerable level, at which point either an additional OAD is added to the treatment regimen or the patient is switched entirely to a new OAD (10). This procedure is continued until treatment options with OADs are exhausted, and the patient is transferred to insulin. Insulin has to be injected subcutaneously instead of being administered orally and may therefore be more uncomfortable for the patient.

Thus, pharmacological treatment recommendations vary across patients and in different situations. In addition, unlike in an acute illness where patients are asked to take a medication, for example three times a day for 10 days, the treatment for diabetes involves a lifelong, complex regimen in which pharmacological therapy forms only a part of the treatment plan. In diabetes, patients are expected to follow a complex set of behavioral actions to manage their diabetes on a daily basis. These actions involve engaging in positive lifestyle behaviors, including following a strict diet and meal plan; engaging in appropriate physical activity; taking medications as prescribed when indicated; monitoring blood glucose levels; and responding to and self-treating diabetes-related symptoms. The regimen is further complicated by the need to integrate and sequence all of these behavioral tasks into a patient's daily routine and to account for the fact that some of these measures may compensate for each other (6).

Physical exercise may reduce the quantity of drugs required to maintain adequate glycemic control, and an extra pill may compensate for small dietary sins such as a cake, sweets or an opulent meal that would otherwise drive blood glucose up beyond the "complications free" threshold level. This may lead to overconsumption relative to prescribed dosages and has been observed by some researchers previously. For example, in a study conducted in the United States Paes et al. (1997) observed that overconsumption of OAD is a common problem and that 30% of diabetes patients consumed more than the prescribed amounts (11). Also Bergman (1978) found that "for the five most common oral anti-diabetic drugs, the average daily dose prescribed was found to be higher (37-132%) than the `daily doses´ used in the international comparison" for a sample of diabetes patients on the island of Gotland, Sweden (21). In Denmark drugs for chronic diseases are usually issued for several refills at a time, so that the patient does not need to see a doctor to refill his or her prescription in order to prevent supply shortages. Prescriptions are transmitted to the pharmacies electronically and patients refill their prescriptions on average about every six to seven weeks.

Thus, taking less medication is not necessarily a sign of non-adherence, but may be an indication that the patient is very adherent to other dimensions of therapy. (In fact, complete remission is not uncommon if weight loss can be achieved with appropriate dietary restrictions and/or physical exercise.[3]) Similarly, taking more than the prescribed medication may mean that the patient is potentially less adherent to meet overall treatment goals. These considerations should ideally be reflected in a meaningful measure of adherence, at least if the measure is to be used as a feedback tool for disease management programs or other surveillance

[3] See UK diabetes association, http://www.diabetes.co.uk/insulin/insulin-sensitivity.html.

programs intended to improve health outcomes of chronic patients. An adherence measure based on a standard that is not patient-specific, such as the defined daily dosages (DDD), is therefore likely to overestimate the extent of true non-adherence, especially near the onset of treatment.

3. Methods

Study population and study design

In this retrospective non-randomized cohort study, patients were identified using the pharmaceutical product registry, which is an electronic record of all prescription drug sales for the entire population residing in Denmark since 1996 (22). The ATC classification system was used to identify patients who consumed oral anti-diabetic drugs (OADs) ATC code A10B during our observation interval. Since one of our key variables, the prescribed dosage, has only been registered since 2005, patients were included if they started treatment with OADs after 2004 and had at least two prescriptions for the same OAD between 2005 and 2011. Thus, the study did not include patients who were diagnosed with diabetes but who were not using medications to treat it, and it did not capture primary non-adherence, which occurs if the patient never fills the first prescription. Information about the date of diagnosis and the date of the start of drug treatment was identified for each patient from the diabetes register using a unique person identifier. We excluded patients with type 1 diabetes, defined as below age 50 receiving insulin from the day of diagnosis.[4] The date of the first prescription of a specific OAD was defined as the index date and marked the beginning of the follow-up period. Hospitalizations and death registers were used to identify health outcomes and population registers were used to link socio-economic characteristics for each patient (22-26). Our records included pharmaceutical expenditures, but no expenditures for hospitalizations or other health care utilization. Patients were de-identified in compliance with Danish data protection laws, and the study was approved by the Danish data protection agency.

Health outcomes

The primary outcomes analyzed were all-cause hospitalization and all-cause mortality during the follow-up period (January 1, 2005, through December 31, 2011). Data on hospitalizations were derived from the Danish inpatient register (25). Patients were defined as hospitalized if they were admitted to a hospital

[4] We excluded type 1 diabetes patients because they are usually much younger and they are mainly treated with insulin for which data on prescribed dosages were unavailable.

(inpatient admission) for any condition between the start of treatment and the end of the observation period. If a diabetes patient had died, the date of death is recorded in the diabetes register. To analyze mortality, patients were identified as dead if they died anytime during the follow-up period. Finally, longevity was defined as the total lifetime of the patient (from birth), identifying patients who had not died by December 31st 2011, as (right) censored.

Adherence to drug therapy

As adherence can differ between different aspects of care, we define adherence to drug therapy by treatment episode as a unique drug-patient combination, using the WHO-defined ATC code (level 5) to identify pharmaceutical substances (27). Adherence to a specific therapy was measured as the medical possession ratio (MPR) over the entire treatment interval. The MPR is based on an "availability of drugs approach" and measures the extent to which the patient had sufficient supplies of a drug on hand to potentially comply with therapeutic recommendations (28). It is a continuous measure calculated by dividing the number of days' supply contained in a pharmaceutical prescription by the number of days between the present and subsequent refill. Days' supply was calculated in two ways: first, by dividing the number of pills contained in a refill by the actually prescribed daily dosage; or alternatively we used the defined daily dosage (DDD) instead of the actually prescribed dosage. "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults" (9), and is therefore drug-specific but not patient-specific.[5] Especially when prescribed dosages vary over the course of treatment and across individuals, DDDs may not reflect patients' true adherence very accurately. Nevertheless, DDDs have been used in numerous previous studies to assess patient adherence to pharmacotherapy (29-33). To obtain an overall ratio for the entire treatment episode, interval MPRs were combined, taking leftover stock into account. It was calculated by dividing the total number of days' supply purchased minus the supply in the last refill by the number of days between the first and last refill date. As the extent of patient adherenc3e following the last prescription was unknown, the last prescription was excluded from the analysis.

In addition, we formed a categorical variable stratifying patients into five adherence categories based on their score for the medical possession ratio over the entire period: ≤70%, 70%-≤90%, 90%-≤110%, 110-

[5] For substances such as A10B07 that did not have a WHO assigned DDD value, we used the values assigned by the Danish Medicines Agency.

≤130%, and >130% to investigate whether the relationship between adherence and health outcomes is indeed monotone. This was done for the medical possession ratio based on individual prescribed dosages (MPR_PD) as well as DDD (MPR_DDD). Finally, we formed a dichotomous indicator for adherent patients equal to one if the patient deviated by less than 10% from the prescribed dosage (i.e., fell into the middle of the five adherence categories). This measure is able to account for potential overconsumption, unlike the cut-off point of 80% that is often used in the adherence literature to split patients into bad and good adherers.[6]

Other covariates

In order to account for demographic characteristics and socio-economic status, we controlled for patients' age, gender, and education. Education was divided into three categories, classifying patients according to their highest educational attainment as no-vocational, vocational, and higher tertiary education. Patients' number of comorbidities, time since diagnosis, and an indicator variable for insulin dependence of the patient at the index date were used to control for disease severity that may influence health outcomes. In addition, we included a linear time trend to account for differences in observation time.

Comorbidity was calculated using a pharmaceutical comorbidity index (PCI) based on patients' prescription drug claims in the year preceding the start of the treatment episode. The PCI is a composite measure of drug utilization across a broad range of chronic conditions; it is based on a modified RxRiskV index and identifies the 19 most prevalent comorbidities in diabetes patients. Table A1 in the appendix lists the ATC codes and associated comorbidities included in the PCT. It has been validated in previous studies to predict healthcare utilization (34-36). The PCI differs from the Charlson comorbidity index with respect to data source (drug vs. medical claims) and the medical conditions which they assess (5).[7]

In addition, for the secondary analysis investigating the determinants of medication adherence, we defined: Cost per day of therapy defined as the average out-of-pocket copayment paid by the patient for one day of drug therapy, dose per day defined as the average number of pills prescribed during a treatment

[6] Although this has become a convention in the adherence literature, this cut-off level has never been empirically validated for diabetes, and in fact Karve et al. (2009) suggest that a level of 89% may be more applicable to predict all-cause hospitalization for diabetes patients (16).

[7] The PCI is especially more sensitive to mental conditions than the Charlson index. The two comorbidity measures also differ with respect to their intended use. The PCI was developed to predict hospitalizations and other measures of health care utilization, whereas the Charlson comorbidity index has been developed for a general population and is based on estimates of survival. It includes more severe, diseases such as HIV which are not particularly prevalent in a diabetes population.

episode, and drug vintage identified as the first year when a drug with a specific ATC code was available in the Danish market.[8] We seek to test the hypothesis that, ceteris paribus, people using newer, or later vintage, medicines are more adherent because newer medicines are typically easier to use. This hypothesis is predicated on the idea that these goods and services, like other R&D-intensive products, are characterized by embodied technological progress (37).

Statistical Analysis

Hospitalization and mortality rates

Multivariate logistic regression was used to estimate hospitalization and mortality rates. It was hypothesized that the probability of being hospitalized or dying during our observation period is higher when adherence to drug therapy is weak. In the logit model the log odds of the outcome is modeled as a linear combination of the predictor variables. Let $\pi_{id} = Pr_{id}(Y_{id} = 1)$ be the probability that patient i is either hospitalized or died during the observation period after starting treatment with drug *d*. Then the odds of the outcome are defined as the probability that the outcome of a particular patient is a case $(Y_{id} = 1)$ divided by the probability that the outcome is no case $(Y_{id} = 0)$.

$$odds_{id} = \frac{\pi_{id}}{1 - \pi_{id}}$$

To model the odds of being hospitalized or dying we use versions of the following model:

$$log\left(\frac{\pi_{id}}{1-\pi_{id}}\right) = \beta_0 + \beta_1 \text{adherence}_{id} + \gamma X_{id} + \gamma t_{id} + \gamma d + \varepsilon_i \quad (1)$$

$\pi_{id} =$ probability that patient i is hospitalized or died

$adherence_{id} =$ measure of medication adherence to drug d by patient i

$X_{id} =$ a vector of attributes of individual i at time of treatment start with drug d

$t_{id} =$ time since start of treatment with drug d

[8] Market authorization dates were identified from documentation about drug licensing from EMA and the Danish Medicines Agency.

$d =$ drug fixed effect

$\varepsilon_{id} =$ disturbance term

Longevity

The logistic regression models do not take the timing of the negative events into account. Thus, in order to take the timing of death into account we estimate a number of survival models based on the general form:

$$ln\ (time\_to\_death_i) = \beta_0 + \beta_1 \text{adherence}_{id} + \gamma X_{id} + \gamma d + \varepsilon_i \quad (2)$$

$$where\ time\_to\_death_i = \text{the number of years until the date of death of individual } i$$

$adherence_{id}$ and X_{id} are defined as in eq. (1) above and represent different continuous, categorical, or dichotomous measures of medication adherence and patient attributes, such as age, gender, education and disease severity at the start of the treatment episode, respectively.

We are able to track a patient's vital status for up to seven years until December 31st 2011. If patient i did not die by December 31st 2011, his or her death date is unknown – we only know that the date of death is after December 31 st 2011. Hence, the variable *time_to_death* is right-censored. We estimate versions of eq. (2) using a statistical procedure (STATA command streg) which fits parametric models to survival time data that can be censored or truncated.[9] We assume that the number of years until the date of death follows a Weibull distribution, one of the most commonly used distributions in failure time analysis.

Our hypothesis is that longevity (or time to death at a given age) is positively related to drug adherence. We investigate the effect of adherence to oral anti-diabetic drugs by an individual patient on his or her longevity (time to death), controlling for several demographic and socio-economic characteristics and indicators of health status. Based on a sample of patients that had not died at the start of our observation period, this method identifies and quantifies determinants of observed differences in the time to patients'

[9] Censoring is defined as a period under which the event (death) occurs but the patient is not observed. Patients are for example right censored if they die after Dec. 31st 2011. Truncation is defined as a period under which the patient was not observed, but is a posteriori known not to have died. Left truncation occurs if a patient enters the study after the onset of risk (birth) and therefore is not observed initially until the start of OAD treatment. Patients whose observations are censored or truncated contribute to the estimation of the hazard function only while being observed and censoring occurs randomly.

deaths. A key concept in duration analysis is the hazard function defined as the rate of death at a specific point in time, given that the individual has not died until that time t $\lambda(t) = \frac{f(t)}{S(t)}$. The observed length of the time interval until death is then explained by a number of individual factors, which shift the hazard function up or down. The hazard function of a Weibull random variable *t* assumes monotone hazard rates and can be written as:

$$\lambda(t) = \lambda p(\lambda t)^{p-1}$$

where $\lambda > 0$ is the scale parameter and $p > 0$ is the shape parameter. The hazard is rising if $p > 1$, constant if $p = 1$, and declining if $p < 1$. The Weibull model can be expressed in a proportional hazard metric with a baseline hazard function, $\lambda_0(t) = \lambda p(\lambda t)^{p-1}$, which is shifted by the proportionality factor $exp(x'\beta)$ representing the relative risk of patient i in relation to the baseline hazard. Thus, the patient's individual attributes shift the hazard in proportion to the baseline according to:

$$\lambda(t, x) = \lambda_0(t) exp(x'\beta)$$

Since $\lambda(t)$ is a parametric distribution we can estimate the individual patient's survival time based on the estimated parameters and the patients' values for the covariates and calculate the mean survival time (as the integral of the survival function $S(t)$) for different groups of patients.

Determinants of adherence to therapy

Finally, we use a logistic regression model to investigate which factors are associated with better adherence to drug therapy. In this case $\pi_{id} = Pr_{id}(Y_{id} = 1)$ is the probability that the patient deviates less than 10% from the prescribed dosage (is adherent to drug therapy) when consuming drug *d*.

$$logit(\pi_{id}) = \log\left(\frac{\pi_{id}}{1-\pi_{id}}\right) = \alpha_0 + \alpha_1 drug\_vintage_d + \delta Z_{id} + \delta t_{id} + u_{id} \quad (3)$$

$drug\_vintage_d =$ is a measure of the vintage of the drug d

$Z_{id} =$ a vector of attributes of individual i for the treatment with drug d

$t_{id} =$ time since start of treatment with drug d

$u_{id} =$ disturbance term

Z_{id} includes the average out-of-pocket costs for drug *d* per day of therapy, the average number of pills patient i should take of drug *d* per day, age, gender, education, and measures of disease severity at time of treatment start with drug *d*.

Sensitivity analysis

Lacking a consensus for a clinically important level of drug adherence, we investigated the consistency of our estimates by defining adherence categories based on quintiles of the adherence distribution to explore the sensitivity of our models with respect to changes in threshold levels. Moreover, as a result of the study design there was an overlap of the intervals during which both outcomes and the adherence predictors were measured. In order to rule out a simultaneity bias,[10] we calculated an alternative measure of the medical possession ratio in which we subtracted the number of days spent in hospital from the time intervals between refills (this is equivalent to assuming that adherence was perfect during periods of hospitalization and is supplied by other sources, whereas the other approach assumes that the patient used his or her own drug purchases during periods of hospitalization) to evaluate whether this affected our results. Finally, we assessed how the assumption about the onset of risk in the survival analyses affected our results by setting onset of risk to time of diagnosis instead of time from birth. The results of these sensitivity analyses are consistent with our findings presented in the following section. Due to space limitations, precision of estimates and interpretability in terms of policy implications we selected the models presented in the following section, additional results are available from the authors upon request. All statistical analyses were conducted using STATA 14 software package.

4. Results

Description of the study population

Table 1 presents summary statistics for the study population. The mean age at start of treatment was 63.3 years, and 58% of the sample was male. Patients had on average 3.7 comorbidities, they had on average

[10] Simultaneity bias is a kind of endogeneity bias caused by reverse causality or measurement error, for example if (measured) drug adherence is lower because the patient is hospitalized.

been diagnosed with diabetes 2.3 years earlier, 56% had an inpatient hospital admission during our observation period, and only about 12% of the sample died before January 1st 2012.

Table 1: Characteristics of the study population

Characteristic	Mean	SD
Age	63.3	11.24
% male	58.30	49.30
Number of comorbidities	3.69	2.22
% heart disease	70.85	45.44
% insulin dependent	2.24	1.48
Time since diagnosis in years	2.32	2.68
Refills per year	8.13	9.25
% ≥ 1 diabetes-related complication	8.12	27.31
% ≥ 1 inpatient hospitalization	56.18	49.62
% died	11.91	32.91

Comparison of different adherence measures across substances

Table 2 shows the average level of adherence to OAD drugs across pharmaceutical substances for six measures of adherence, which may be used to assess the extent of non-adherence to OADs in the Danish population. Adherence varies considerably across substances and across adherence measures, which implies that the assessment of the extent of non-adherence is very sensitive to the method used. The first three rows refer to the overall adherence to OAD therapy across all substances. The rows below report adherence levels to the specific substances. For most oral anti-diabetic drugs adherence is much higher if measured using the actual prescribed dosage (column 1) than the WHO-defined DDDs (column 2). This indicates that on average the prescribed dosage is lower than the standard drug-specific DDD. Columns 3 and 4 indicate the percentage of diabetes patients who would be considered adherent to therapy if a cut-off point of >80% of the MPR was used to identify good adherers. This measure is only reported to enable comparability of our results to previous studies that have used this measure to assess adherence to OADs in other populations. Using this measure

80.1% of diabetes patients would be considered as good adherers if the prescribed dosage is used as the target adherence level, whereas only 44.4% would be considered good adherers if DDDs were used as the target level. However, this measure neglects the issue of overconsumption, as for example indicated in column 1. Average adherence is above 100% and the standard deviation is high. This can also be seen from columns 5 and 6. The former indicates that only 45.9% of diabetes type 2 patients deviate less than 10% from the prescribed dosage on average (or conversely that more than half of the patients deviate more than 10% from their recommended drug treatment regimen). Only 20% of the patients deviate less than 10% from the WHO-defined DDD.

The rows below indicate that adherence varies considerably across substances. The average MPR to prescribed dosages varies between 85.3% for acarbose (A10BF01) and 146% for linagliptin, and whereas 59.6% of patients taking sitagliptin deviate less than 10% from the prescribed dosage, only 32.6% of patients taking acarbose deviate less than 10% from their dosage regimen.

For metformin (ATC code A10BA02), by far the most widely used OAD, the medical possession ratio is on average 100%, suggesting that adherence is on average quite good and that using DDD values (column 2) may overstate non-adherence in the Danish diabetes type 2 population.

Table 2: Comparison of adherence measures using prescribed dosage (PD) and DDDs

Substance **No. obs.**		**MPR_PD**	**MPR_DDD**	**MPR_PD >80**	**MPR_ DDD >80**	**90%< MPR_PD <110%**	**90%< MPR_DDD <110%**
Total	Mean	1.040	0.813	0.801	0.444	0.459	0.202
N=196938	SE mean	0.003	0.002	0.001	0.001	0.001	0.001
	SD	1.182	0.916	0.400	0.497	0.498	0.401
metformin	Mean	1.001	0.653	0.765	0.307	0.426	0.149
A10BA02	SE mean	0.003	0.001	0.001	0.001	0.001	0.001
N=116095	SD	0.964	0.441	0.424	0.461	0.495	0.356
glimepiride	Mean	1.134	1.142	0.863	0.620	0.475	0.166
A10BB12	SE mean	0.007	0.007	0.002	0.002	0.002	0.002
N=42830	SD	1.535	1.508	0.344	0.485	0.499	0.372
sitagliptin	Mean	1.024	1.022	0.875	0.877	0.596	0.599
A10BH01	SE mean	0.005	0.004	0.003	0.003	0.005	0.005
N=9335	SD	0.444	0.425	0.331	0.329	0.491	0.490
gliclazide	Mean	1.106	0.909	0.859	0.461	0.501	0.150
A10BB09	SE mean	0.020	0.015	0.004	0.006	0.006	0.005
N=6152	SD	1.544	1.158	0.348	0.499	0.500	0.357
met &vilda	Mean	0.957	0.957	0.816	0.819	0.584	0.589

A10BD08	SE mean	0.005	0.005	0.006	0.006	0.007	0.007
N=4898	SD	0.340	0.328	0.388	0.385	0.493	0.492
glibenclamide	Mean	1.138	0.748	0.834	0.369	0.405	0.142
A10BB01	SE mean	0.016	0.015	0.006	0.008	0.008	0.006
N=3991	SD	0.996	0.947	0.372	0.483	0.491	0.349
met &sita	Mean	0.951	0.950	0.812	0.813	0.570	0.574
A10BD07	SE mean	0.005	0.005	0.006	0.006	0.008	0.008
N=3942	SD	0.300	0.294	0.391	0.390	0.495	0.495
glipizide	Mean	1.288	0.714	0.890	0.345	0.385	0.155
A10BB07	SE mean	0.028	0.013	0.006	0.010	0.010	0.007
N=2490	SD	1.401	0.665	0.313	0.476	0.487	0.362
met &rosi	Mean	0.954	1.071	0.760	0.819	0.533	0.496
A10BD03	SE mean	0.029	0.030	0.009	0.008	0.010	0.010
N=2330	SD	1.419	1.441	0.427	0.385	0.499	0.500
vildagliptin	Mean	0.975	0.972	0.742	0.742	0.504	0.506
A10BH02	SE mean	0.022	0.026	0.013	0.013	0.015	0.015
N=1168	SD	0.748	0.874	0.438	0.438	0.500	0.500
tolbutamide	Mean	1.069	0.819	0.793	0.411	0.430	0.147
A10BB03	SE mean	0.025	0.019	0.012	0.015	0.015	0.010
N=1143	SD	0.859	0.639	0.406	0.492	0.495	0.354
saxagliptin	Mean	1.141	1.011	0.890	0.843	0.571	0.552
A10BH03	SE mean	0.093	0.014	0.010	0.011	0.015	0.015
N=1050	SD	3.025	0.438	0.312	0.364	0.495	0.497
rosiglitazone	Mean	1.297	1.081	0.845	0.425	0.546	0.101
A10BG02	SE mean	0.185	0.146	0.013	0.017	0.017	0.01
N=824	SD	5.302	4.180	0.362	0.495	0.498	0.301
acarbose	Mean	0.853	0.471	0.591	0.096	0.326	0.052
A10BF01	SE mean	0.023	0.013	0.029	0.017	0.028	0.013
N=291	SD	0.398	0.224	0.492	0.295	0.470	0.221
pioglitazone	Mean	1.124	0.823	0.844	0.502	0.436	0.253
A10BG03	SE mean	0.042	0.030	0.021	0.029	0.029	0.026
N=289	SD	0.717	0.503	0.363	0.501	0.497	0.435
linagliptin	Mean	1.467	1.431	0.948	0.959	0.433	0.454
A10BH05	SE mean	0.123	0.119	0.023	0.020	0.051	0.051
N=97	SD	1.210	1.173	0.222	0.200	0.498	0.500
glime &rosi	Mean	0.996	1.001	0.923	0.923	0.538	0.615
A10BD04	SE mean	0.076	0.075	0.077	0.077	0.144	0.140
N=13	SD	0.273	0.271	0.277	0.277	0.519	0.506

Distribution of drug adherence across adherence categories

Figures 1A and 1B show the distribution of drug adherence across categories defined by deviations from the individually prescribed dosage or standard drug-specific DDD values for all substances combined. Figure 1A shows that on average about 45.9% of the patients deviate less than 10% from the prescribed dosage. Whereas about 15% of diabetes patients take less than 90% and 14% take less than 70% of the prescribed dosage, and about 12% take more than 110% and 130%, respectively.

Figure 1B indicates that 48.5% of the patients take less than 70% of the DDD, 15.8% take between 70% and 90% of the DDD, 19.6% deviate less than 10% from the DDD and 5.7% and 10.1% consume more than 110% and 130% of the official DDD, respectively.

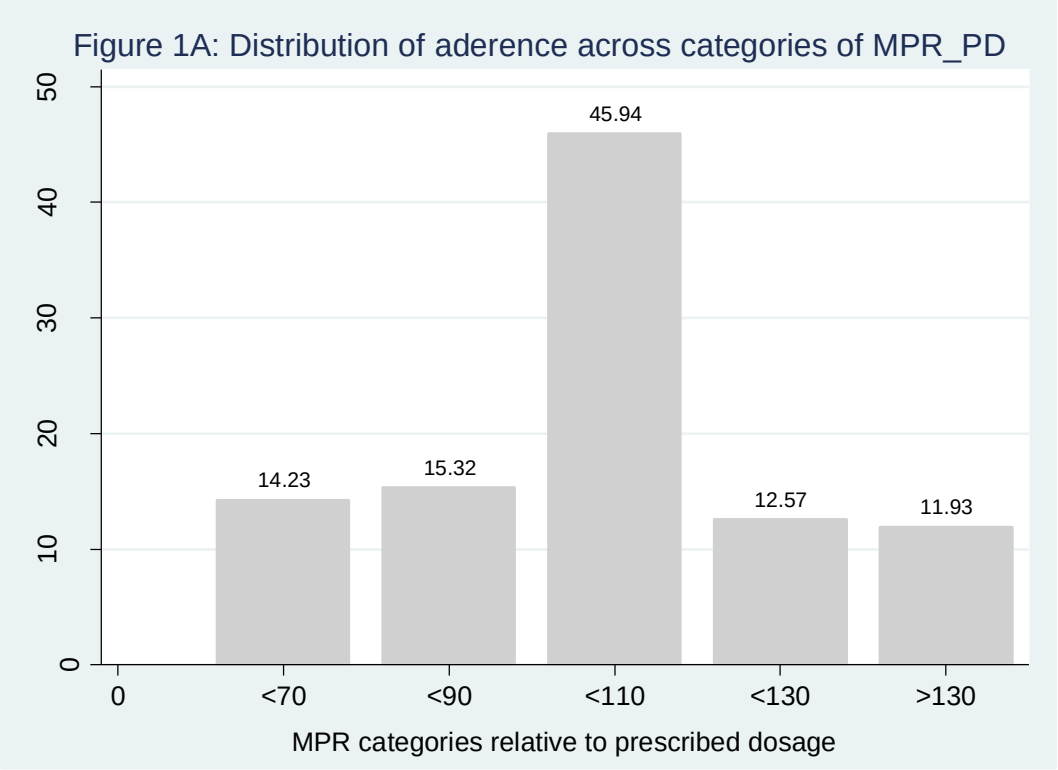
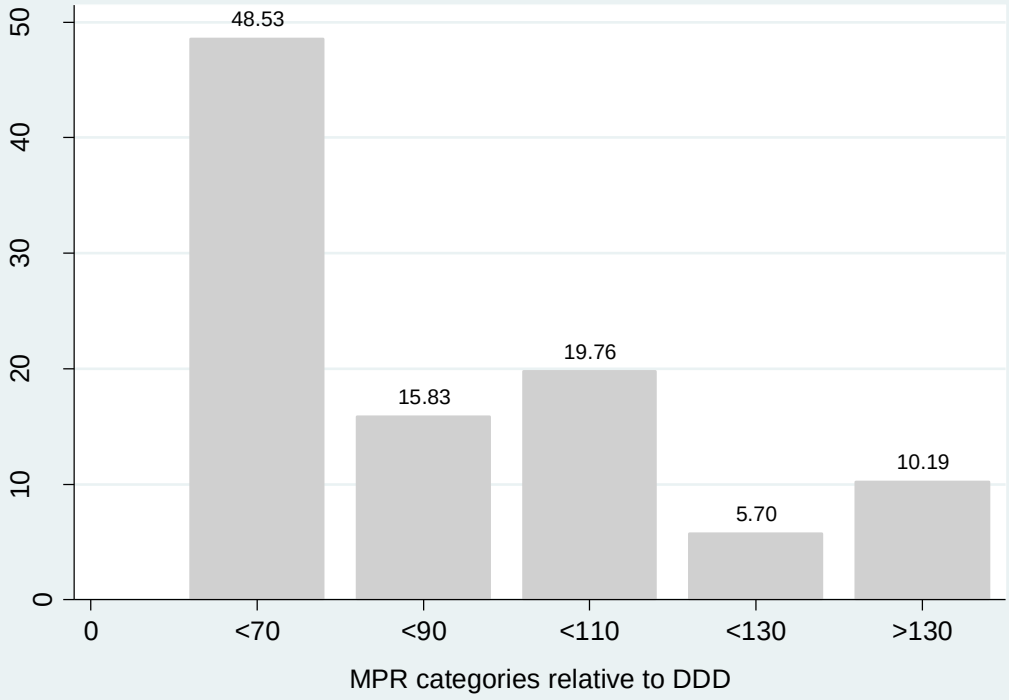


Figure 1B: Distribution of adherence across categories of MPR_DDD



Regression results

To limit the influence of outliers on our regression estimates we only included observations that were within the 1st and 99th percentile of the distribution of the respective continuous measure of the medical possession ratio.

Hospitalization rates

Table 3 shows estimates of the odds of being hospitalized after the start of the respective OAD treatment using logistic regression for different measures of drug adherence. The explanatory variables of primary interest are our measures of adherence to drug therapy. In all regressions we control for age, gender, education, insulin dependency, number of comorbidities, and time since diagnosis at the date of initiation of the treatment episode to control for disease severity and demographic characteristics that may affect health outcomes and time since treatment start.

Table 3: The impact of adherence on any inpatient hospitalization using logistic regression

		Prescribed Dosage			WHO Defined Daily Dosage		
Hospitalization		**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
Variable	Statistic	Continuous	Dichotom	Categorical	Continuous	Dichotom	Categorical
MPR	Odds ratio	**0.9459**			**1.1479**		
	robust std. err	0.0164			.01687		
	P-value	0.001			0.000		
MPR < 70%	Odds ratio			**1.1306**			**0.9450**
	robust std. err			.0200			.0146
	P-value			0.000			0.000
70% < MPR < 90%	Odds ratio			**1.2398**			**1.0806**
	robust std. err			.0194			.0197
	P-value			0.000			0.000
90% < MPR < 110%	Odds ratio		**0.8879**	**1**		**.9956**	**1**
	robust std. err		.0097			.0141	
	P-value		0.000			0.758	
110% < MPR < 130%	Odds ratio			**1.0347**			**1.0651**
	robust std. err			.0175			.0276
	P-value			0.044			0.015
130% < MPR	Odds ratio			**1.0710**			**1.0804**
	robust std. err			.0197			0.0253
	P-value			0.000			0.001
	Pseudo R^2	0.0971	0.0976	0.0980	0.0974	0.0971	0.0976
	Log likelihood	-102386	-102231	-102185	-102344	-102185	-102133

Number of observations 165413 (Std. err. adjusted for 117767 clusters in patient id)

We controlled for age, male gender, education, number of comorbidities, insulin dependence, time since diagnosis at the date of first prescription (start of the treatment episode), time since treatment start as well as substance fixed effects. The control variables all had the expected sign; male gender and education were associated with lower hospitalization rates, while all other control variables were associated with higher hospitalization rates.

Model 1 includes the medical possession ratio based on prescribed dosage (MPR_PD) as a continuous measure of drug adherence. Model 1 assumes that there is a linear relationship between the MPR_PD and hospitalizations and indicates that a higher medical possession ratio is associated with lower risk of being hospitalized. In Model 2 we dichotomize the medical possession ratio defining patients as adherent if they do not deviate (in either direction) by more than 10% from the prescribed dosage. The estimates indicate that the odds of being admitted to a hospital are about 11.2% lower for patients who follow the drug prescription plan more closely compared to other patients. In Model 3 we divide patients according to their medical possession

ratio into 5 categories (below 70%, 70≤90%, 90–≤110%, 110≤130%, and above 130%) to inspect whether the benefits of higher OAD consumption extend over the entire range or whether there is a cut-off point beyond which higher adherence does not provide any additional health benefits. Using patients who follow the prescribed dosage plan most closely as the reference category, we find that patients who consume less than 90% of the prescribed dosage are significantly more likely to be hospitalized. Additionally, consuming more than the prescribed dosage is also associated with an increased risk of hospitalization, although the increase in risk is smaller than for patients taking less than 90% of the prescribed dosage. This is in line with previous literature that found that better adherence is associated with lower risk of hospitalization (2; 5; 17). However, truncating the medical possession ratio at 100% or defining all patients above 80% MPR as adherent patients may bias estimation results.

Models 4 to 6 present the estimation results when DDD instead of prescribed dosage is used as the target value (MPR_DDD). Model 4 indicates that a higher medical possession ratio based on DDD is associated with a higher probability of being hospitalized. Similarly, Model 5 indicates that those who deviate less than 10% from the DDD have no lower probability of being hospitalized. In fact, Model 6 indicates that patients consuming less than 70% of the standard DDD have the lowest risk of hospitalization.

Mortality

Table 4 presents estimates of the odds of dying within our observation time before January 2012 for models using different measures of drug adherence. Models 11–13 include measures of drug adherence based on the prescribed daily dosage, whereas Models 14–16 include measures of drug adherence based on DDD.

Model 11 and Model 14 both indicate that an increase in the medical possession ratio is associated with a higher probability of dying. However, Models 12 and 13 indicate that following the prescribed dosage more closely is associated with a lower probability of death. Deviating from the prescribed dosage by less than 10% decreases the odds of dying during our observation period by about 8%, whereas deviating from the prescribed dosage by more than 10%, both in terms of under- and overconsumption increases the odds of dying during the observation time significantly. These estimates indicate that the linear model is misspecified because the relationship between adherence, measured as MPR based on prescribed dosage, and mortality is rather U-shaped. In fact overconsumption of OADs may be an indication that patients neglect other dimensions of therapy such as diet, exercise or regular doctor's visits. Thus, consuming more than the prescribed amount

of OADs may keep patients' blood glucose levels under control and the patients out of hospital in the short run, but in the long-run disease progression may accelerate, for example due to decreasing drug sensitivity leading to premature death.

Models 14 to 16 indicate that aiming for high adherence to standard DDDs cannot be a treatment goal since it is associated with higher probability of death during our observation period. Patients who consume less than 70% of the standard DDD also have the lowest probability of death. This group of patients may comprise more healthy patients than non-adherent patients. Thus, assessing medication non-adherence using standard DDDs as the target value may lead practitioners astray.

Table 4: The impact of adherence on all-cause mortality using logistic regression

		Prescribed dosage			**WHO Defined Daily Dosage**		
Mortality		**Model 11**	**Model 12**	**Model 13**	**Model 14**	**Model 15**	**Model 16**
Variable	Statistic	Continuous	Dichotom	Categorical	Continuous	Dichotom	Categorical
MPR	Odds ratio	**1.0668**			**1.6124**		
	robust std. err	.0299			.0333		
	P-value	0.021			0.000		
MPR < 70%	Odds ratio			**1.0694**			**0.7027**
	robust std. err			.0336			.0190
	P-value			0.033			0.000
70% < MPR < 90%	Odds ratio			**1.0781**			**.9891**
	robust std. err			.0295			.0321
	P-value			0.006			0.736
90% < MPR < 110%	Odds ratio		**0.9212**	**1**		**1.1589**	**1**
	robust std. err		.0170			.0288	
	P-value		0.000			0.000	
110% < MPR < 130%	Odds ratio			**1.0812**			**1.0951**
	robust std. err			.0295			.0481
	P-value			0.004			0.044
130% < MPR	Odds ratio			**1.1302**			**1.2934**
	robust std. err			.0324			.0453
	P-value			0.000			0.000
	Pseudo R^2	0.1812	0.1813	0.1813	0.1862	0.1811	0.1856
	Log likelihood	-43351	-43275	-43273	-43085	-43207	-429670

Number of observations 165413 (Std. err. adjusted for 117767 clusters in patient id)

We controlled for age, male gender, education, number of comorbidities, insulin dependence, time since diagnosis at the date of first prescription (start of the treatment episode), time since treatment start as well as

substance fixed effects. The control variables all had the expected sign; male gender and education were associated with lower hospitalization rates, while all other control variables were associated with higher hospitalization rates.

Longevity

Table 5 presents the results of survival analyses taking the timing of death, censoring, and truncation of the data into account. Time is measured as time from date of birth in years and patients enter the study when they start treatment with OADs. A hazard ratio greater than 1 indicates that a change in the respective covariate from zero to one increases the hazard of dying, whereas a value between 0 and 1 shifts the hazard rate downward. The estimates of the shape parameter *p* indicate that the baseline hazard of dying is increasing over time in all models. Model 21 indicates that a higher medical possession ratio is associated with a small increase in the hazard of dying. However, assuming linearity is problematic if there is substantial overuse of OAD medication. Model 22 indicates that following the prescribed dosage plan closely results in 25% better survival. Model 23 indicates that the 24.5% of patients consuming more than 110% of the prescribed dosage have an even higher risk of dying than patients consuming less than 90% of the prescribed amounts, resulting in a U-shaped relationship between drug adherence and longevity. Thus, consuming more than the prescribed dosage is particularly harmful, and patients deviating less than 10% from the prescribed dosage are facing the lowest hazard of premature death. Finally, the results of models 24 through 26 indicate that measuring adherence to drug therapy based on DDD does not provide a good indicator for monitoring quality of care.

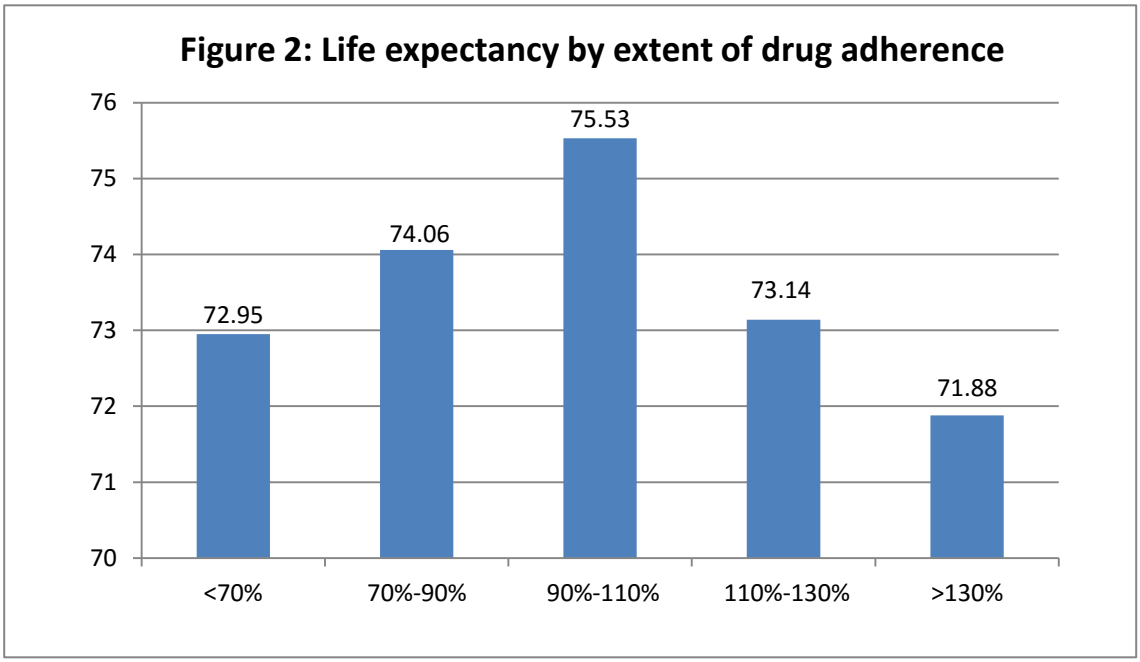
Table 5: The impact of adherence on longevity using survival analysis with a Weibull distribution							
		Prescribed Dosage			**WHO Defined Daily Dosage**		
Longevity		**Model 21**	**Model 22**	**Model 23**	**Model 24**	**Model 25**	**Model 26**
Variable	Statistic	Continuous	Dichotom	Categorical	Continuous	Dichotom	Categorical
MPR	Haz. ratio	**1.0638**			**1.0849**		
	std. err	.0024			0.0058		
	P-value	0.000			0.000		
MPR < 70%	Haz. ratio			**1.1846**			**0.9862**
	std. err			.0299			0.0255
	P-value			0.000			0.590
70% < MPR < 90%	Haz. ratio			**1.1066**			**1.0301**
	std. err			.0258			0.0237
	P-value			0.000			0.197
90% < MPR < 110%	Haz. ratio		**.7404**	**1**		**.9005**	**1**
	std. err		.0112			.0186	
	P-value		0.000			0.000	
110% < MPR < 130%	Haz. ratio			**1.4463**			**0.8443**
	std. err			.0325			0.0209
	P-value			0.000			0.000
130% < MPR	Haz. ratio			**1.7398**			**1.0609**
	std. err			.0385			0.0249
	P-value			0.000			0.012
shape parameter p	Haz. ratio	12.694	13.211	12.815	12.528	12.847	12.662
	std. err	.273	.275	0.273	0.273	0.275	0.274
	P-value	0.000	0.000	0.000	0.000	0.000	0.000
	Log likelihood	7476.0	7151.7	7799.85	7404.2	7113.8	7407.6

We controlled for age, male gender, education, number of comorbidities, insulin dependence at time of treatment start, time since diagnosis as well as substance fixed effects. The control variables all had the expected sign. Higher education was associated with lower hazard rates, while all other control variables were associated with a higher hazard of dying.

Using the estimates of Model 23 we predict the estimated survival time (from date of birth) for every individual.[11] Figure 2 presents these estimates for the five categories of drug adherence based on prescribed dosages. Patients who take less than 70% of the prescribed dosage have a life expectancy that is on average 2.6 years lower than patients who follow their drug treatment schedule more closely. Similarly, patients who

[11] As a sensitivity analysis we additionally estimated time until death from time of diagnosis. Results were consistent with our findings using time from date of birth as outcome measure. However, since the timing of diagnosis may have changed over the course of our observation period, we believe that time from birth is the better measure.

overconsume OADs lose more than 3.5 years in life expectancy compared to adherent patients. For the model without covariates mean survival time is 75.2 years (median 76.4 years). These numbers are consistent with WHO estimates, according to which life expectancy at birth in the general population was 79.8 years in Denmark in 2011 and diabetes type 2 decreases life expectancy by 5–10 years.[12]



Determinants of good drug adherence

Figure 3 shows the share of patients who are adherent; i.e., who deviate less than 10% from the prescribed dosage by drug and launch year of the drug. The bubbles represent the different drugs in our sample. The size of the bubbles represents the number of observations per drug. Fitting a linear regression using the number of observations per drug as weights, we find that drug vintage is positively associated with drug adherence. The coefficient estimate indicates that average adherence increases by about 0.23% for every one year increase in launch year. This means that patients who take drugs that are 10 years newer are on average 2.3% more likely to take their medicines as prescribed.

[12] WHO estimates based on the period life expectancy http://www.who.int/gho/countries/dnk/country_profiles/en/

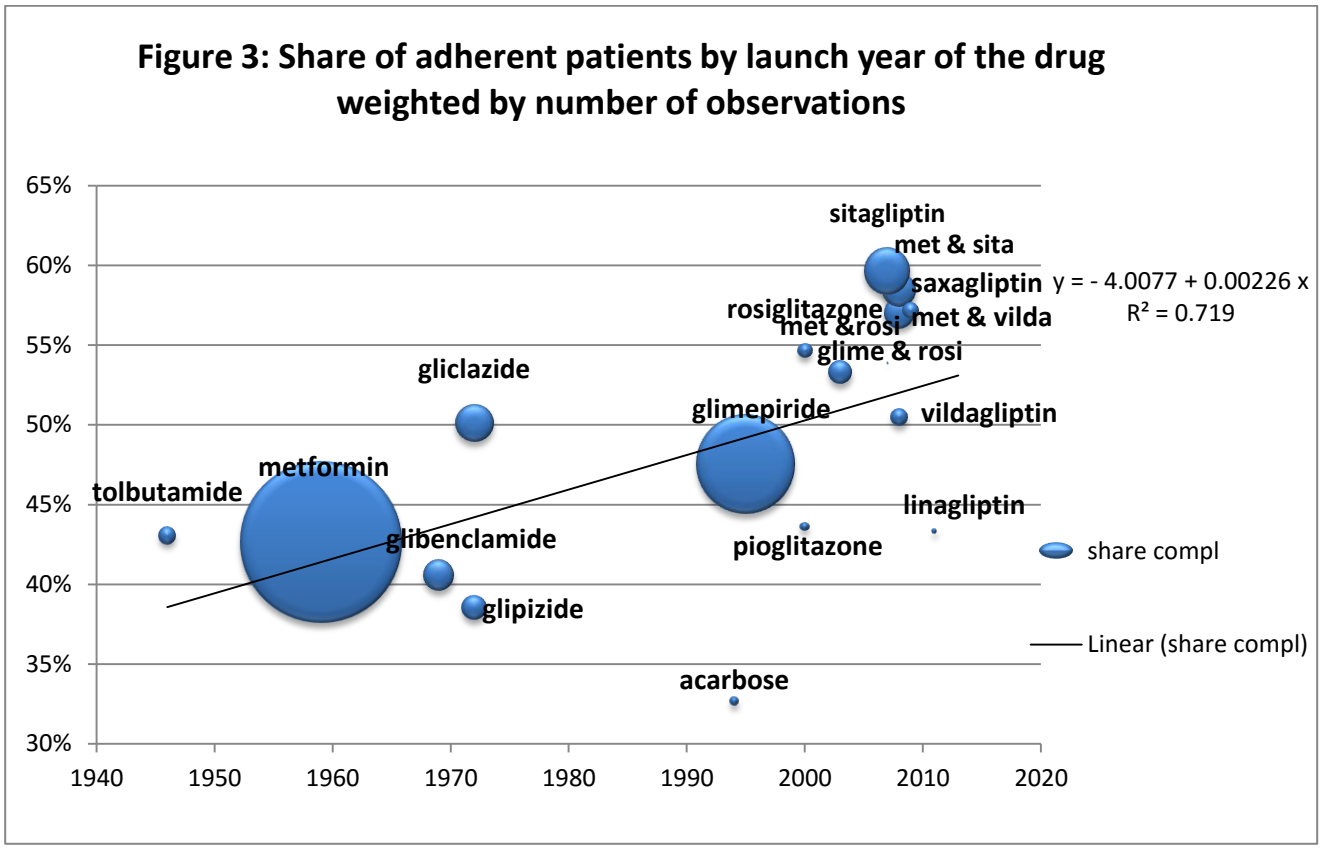


Table 6 presents models of the probability of deviating by less than 10% from the prescribed daily dosage using logistic regression. Models 31 and 32 include the launch year of the drugs normalized to 1970 as a measure of drug vintage. Model 31 includes no other covariates. The estimates indicate that an increase in drug vintage by one year increases the odds of being adherent by about 1%. Evaluated at the mean this means that the probability of adherence increases by about 0.23% per year. The results are therefore very consistent with our linear regression estimates using aggregate data. Model 32 demonstrates that the estimates for drug vintage do not change much when additional covariates are included, which suggests that there is no omitted variable bias.

In models 33 and 34 we dichotomized drug vintage into drugs launched before and after 1995. Model 33 indicates that the odds of being adherent to OAD treatment increase by about 71% for drugs that were launched after 1995 compared to drugs before 1995. Patients who take OADs launched after 1995 have a 13.3% higher probability of deviating less than 10% from the prescribed dosage than patients taking older drugs. Including other covariates increases the estimated effect of vintage on the odds of adherence slightly, which may be due to the fact that drug vintage and costs per day are positively correlated.

Table 6: The impact of drug launch year on adherence to prescribed dosages using logistic regression

90<MPR_PD <110%		Model 31	Model 32	Model 33	Model 34
Variable	**Statistic**	**w/o controls**	**w controls**	**w/o controls**	**w controls**
L_year-1970	Odds ratio	**1.0092**	**1.0125**		
	robust std. err	.0002	.0004		
L_post95	Odds ratio			**1.7124**	**2.0790**
	robust std. err			.0248	0.0416
Pills per day	Odds ratio		**1.0744**		**.9829**
	robust std. err		.0062		.0046
Costs per day	Odds ratio		**1.0068**		.9876
	robust std. err		.0033		.0227
Age	Odds ratio		**1.0199**		**1.0199**
	robust std. err		.0005		.0005
Male	Odds ratio		**.9330**		**.9428**
	robust std. err		.0096		.0097
No edu	Ref. cat.				
Vocational edu	Odds ratio		**1.0399**		**1.0323**
	robust std. err		.0115		.0114
Higher ter. edu	Odds ratio		1.0008		.9904
	robust std. err		.0151		.0149
Time since diag.	Odds ratio		**.9987**		**.9984**
	robust std. err		.0020		.0020
No. comorb.	Odds ratio		.9992		**.9949**
	robust std. err		.0024		.0023
Insulin	Odds ratio		**.9163**		**.9104**
	robust std. err		.0324		.0323
Constant	Odds ratio	**.8247**	**.2230**	**.7952**	**.2691**
	robust std. err	.0040	.0082	.0041	.0096
	pseudo R2	0.0055	0.0144	0.0058	0.0151
	log likelihood	-135002	-120779	-134989	-120700
	Nr. Obs.	196938	177291	196938	177291
	Nr. patients	134968	123912	134968	123912

Models with controls adjust for time since diagnosis, insulin dependence, comorbidities, the average number of pills per day, average out-of-pocket costs per day, patient's age, male gender and education. We did not find a clear relationship between either higher education or number of comorbidities and better adherence. Similarly, higher costs did not seem to impede adherence for the Danish DM population, and a higher number of pills per day (potentially implying more frequent dosages) was not associated with lower medication adherence.

5. Discussion

The current study assessed the extent of clinically important non-adherence to oral anti-diabetic drugs in the Danish population and introduced a new way to measure non-adherence that can easily be implemented in disease management programs to monitor patient adherence to treatment targets in order to prevent long-term adverse health effects. We demonstrated the advantages of the new adherence measure based on deviations from the prescribed dosing regimen using all-cause hospitalizations, mortality, and life expectancy as outcome measures. Medication non-adherence is common and should be directly assessed by health care professionals, such as clinicians and pharmacists. The under-recognition of medication non-adherence can have adverse consequences. Patients who deviated more from the prescribed dosage had worse long-term health outcomes than patients who followed the prescribed dosage more closely.

Our estimates clearly show that the life expectancy of patients who either underuse or overuse oral anti-diabetic medicines is significantly lower than that of patients who use the prescribed amount. The life expectancy of people who consume less than 70% of the prescribed amount is 2.5 years lower. The life expectancy of people who consume more than 130% of the prescribed amount is 3.6 years lower. We are unaware of any previous investigations that demonstrated an association between adherence to drug therapy and longevity in unselected diabetes type 2 populations. Our finding of links between medication adherence and hospitalization, mortality, and longevity expands the literature on adherence and emphasizes the importance of medication non-adherence in clinical practice. Our findings on hospitalizations are consistent with findings in previous studies, which showed that low adherence leads to higher hospitalization rates. However, it is an important novelty of this study not only to assess the impact of under- but also overconsumption, which has been neglected in the (health economic) literature on medication adherence.

Moreover, we demonstrate that at least in the case of oral anti-diabetic medicines, the WHO DDD is a seriously flawed measure of optimal consumption. Since DDDs are not patient-specific and consumption of OADs tends to increase over time, MPR_DDD may be a measure of unobserved disease progression instead of a measure of adherence to drug therapy. In addition, using DDDs as the target value can lead to a couple of biases in cohort studies resulting from a change in patients' classification of adherence over the treatment course (such as time-window bias, a problem which is alleviated by our method, as the probability of classifying patients as adherent does not change significantly over the treatment episode). Our measure takes the epidemiology of diabetes disease better into account than the measures that are most commonly used in the

adherence literature until today classifying all patients who consume at least 80% of the targeted amount as good adherers. Nevertheless, our study has a number of potential limitations. First, similar to other investigations of adherence using pharmacy refill rates, primary non-adherence could not be assessed, medication consumption was assumed, and the timing of the doses of medications was unknown. Thus, we cannot (explicitly) account for the accuracy of medication sequencing, which is an important part of diabetes treatment regimens. Nevertheless, pharmacy refill records enable electronic adherence monitoring and are correlated with a wide array of clinical outcomes (17). In addition, the act of refilling a prescription is the first step toward taking a medication and reflects a patient's active decision to continue with therapy (38). Second, it is a caveat of our study that we can only measure non-adherence to pharmaceutical treatment. Ideally we would like to measure overall health status and deviations from non-pharmaceutical treatment as well. Some previous studies on heart disease have reported that patients who were more adherent to placebo also showed improved health outcomes, which may indicate that patients who are adherent to medication are also more adherent to other dimensions of care (17). We are unable to disentangle the effect of pharmaceutical treatment adherence from other dimensions of care, such as lifestyle recommendations or eating patterns. Thus, adherence to pharmaceutical treatment defined as deviations from prescribed dosage may be a proxy for overall treatment adherence.

Like most previous investigators of adherence, we cannot account for unobserved patient heterogeneity. This could bias our estimates (upwards) if patients who adhere more closely to the prescribed dosages have unobservable traits, for example genetic factors, that also make them less likely to be hospitalized. A study by Roebuck et al. (2011) indicates that adherence estimates on health care utilization from pooled linear regressions are slightly upwardly biased compared to estimates with patient fixed effects (4). However, they do not account for differences in drug selection, which were included in our analysis through drug fixed effects, and which may well be driving their observed bias. Running a sensitivity analysis not controlling for drug fixed effects showed that estimates of adherence on health outcomes were larger (although less precise), which suggests that drug selection influences health outcomes. In our analysis we control for many factors that are known to be associated with health outcomes and for differences in drug choice; it is therefore not clear what such residual unobserved factors could be.

The reduction in life expectancy may therefore not be entirely due to medication underuse or overuse per se, since patients who are not adherent to medication therapy may also be non-adherent to other (unmeasured) aspects of treatment. But medication adherence (or lack thereof) is a good predictor of longevity

and is a variable that (in principle) could be monitored, and perhaps even influenced, by the health care system. Thus, it may not be a problem for the routine implementation of our new adherence measure as a tool in quality management programs, which was one of the goals of this study. For this purpose it is to a large extent irrelevant whether it is a proxy for overall treatment adherence or only medication adherence, as long as it provides a timely measure that pharmacists and physicians can act upon. Thus, in terms of policy implications, an integration of administratively generated adherence monitoring in disease management programs as deviations from optimal treatment levels may be important for improving survival of diabetes patients in the long-run. Currently, there is a narrow focus on blood glucose levels and other short-term outcome measures. The health system should monitor adherence and intervene when patients deviate substantially from the prescribed dosage. Pharmacists could, for example, get feedback on patients' drug adherence in form of a traffic light system; signaling green if the patient's refill pattern indicates a MPR between 90 and 110%, yellow if the patient is deviating by more than 10% but less than 30% of the prescribed dosage, and red if the patient fills his or her prescription much too early (implying a MPR>130) or much too late (implying a MPR<70%) and provide counseling for the patient reiterating the importance of medication adherence. This should be relatively easy to implement in the Danish health care system, as Denmark has electronic prescribing, and when patients pick up their medication, the pharmacist can see when the previous prescriptions have been filled regardless of which pharmacy they went to.

Finally, patient adherence to therapies has been announced as the next frontier in quality improvement (39). Healthcare systems all over the world are looking for ways to increase patient adherence to medication. We therefore explored the factors that are associated with better adherence in order to give some direction for policy implications on which interventions may be effective in improving patient adherence. Interestingly, we did not find any relationship between better adherence and financial or socio-economic factors. We did not find a clear relationship between education and drug adherence (patients with higher tertiary education are not more adherent than patients with no vocational training) nor any evidence that higher out-of-pocket payments are associated with lower adherence. This is in contrast to findings from a study conducted recently in the United States (40) and may be due to a different definition of medication adherence (MPR≥80%), but could also reflect the specific situation in Denmark. Our findings of a lack of a significant effect of income on adherence is in line with a previous study that investigated the determinants of medication adherence in Denmark but did not consider the potential impact of pharmaceutical innovation (41). Due to a regressive co-payment scheme, based on annual personal pharmaceutical expenditure, chronic patients in

Denmark are relatively well protected from an excessive financial burden of out-of-pocket costs for pharmaceuticals.

In contrast, one pathway to improve adherence may be the choice of medication by the physician. As diabetes is a complex disease, innovation that can make treatment easier is likely to improve adherence. Our results show that patients are more adherent to newer drugs. This may be a factor that improves patient outcomes, which is not captured in randomized clinical trials (where adherence to therapy is closely monitored and therefore near perfect for all treatments), and that physicians may want to consider when choosing which drugs to prescribe. More research on these issues, and further exploration of patient heterogeneity in adherence and unobserved selection, is needed.

Reducing under- and overuse of OADs could be quite valuable: a World Health Organization program considers interventions whose cost per quality-adjusted life year (QALY) gained is less than three times per capita GDP to be cost-effective and those whose cost per QALY gained is less than per capita GDP to be highly cost-effective (42). Denmark's per capita GDP is about 60,000 USD, and monitoring of patient medication adherence may not be very costly to implement in Denmark. However, health policy makers may need to consider with whom the responsibility to react to information on poor medication adherence should be placed-with the pharmacists[13] or the GP - and how to incentivize such monitoring.

6. Conclusion

Monitoring patients' drug adherence is an important means by which quality management programs could improve the health outcomes of chronic diabetes patients. The present analysis provides a number of novel findings advancing the literature on adherence as well as on under- and overuse of medical technology. First, adherence should be measured by comparing actual consumption to patient-specific prescribed amounts, not to DDDs defined by the WHO, which are not patient-specific. Due to a long follow-up period, we are able to estimate the impact of adherence on long-term health outcomes, such as hospitalizations, mortality, and life expectancy, which is arguably the single most important measure of health outcomes. Patients who adhere most closely to the prescribed dosage of oral anti-diabetic medications live longer and are less likely to be hospitalized. The life expectancy of patients who consume less than 70% of the prescribed amount is 2.5 years

[13] For example, how pharmacies could be incentivized to provide counseling for patients that are overconsuming oral anti-diabetic drugs.

lower, and the life expectancy of patients who consume more than 130% of the prescribed amount is 3.6 years lower. About 14% of people consume less than 70% of the prescribed amount, and 12% of patients consume more than 130% of the prescribed amount. Moreover, our estimates indicate that patients using newer drugs tend to adhere more closely to their prescribed treatment regimen.

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Appendix

Table A1: Comorbidities and associated ATC codes included in the pharmaceutical comorbidity index for diabetes patients	
Disease	**ATC Code**
Anti-coagulant therapy	B01AA, B01AB, B01AD, B01AE, B01AX
Anti-platelete therapy	B01AC, C04AD03
Anxiety	N05BA, N05BB, N05BC, N05BD, N05BE, N05BX
Cancer/malignancies	L01, L03AA, A04AA
Cardiac disease anti-arrhythmica	C01AA, C01BA, C01BB, C01BC, C01BD, C01BG, C01EB10
Chronic airway disease / respiratory illness	R03AC, R03AH, R03AK, R03BA, R03BB, R03BC, R03BX, R03CB, R03CC, R03CK, R03DA, R03DB, R03DC, R03DX
Congestive heart failure	C03CA, C03CB, C03CC, C03DA, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C01CA07, C01CE01, C01CE02, C01EB09
Depression	N06A
Gastro-oesophageal reflux disorder	A02B
Glaucoma	S01E
Hyperlipidemia	C10AA, C10AB, C10AD, C10AX, C10BA, C10BX
Hypertension	C02AC, C02BA, C02BB, C02CA, C02CC, C02DA, C02DB, C02CB, C02DD, C02DG, C03AA, C03AB, C03AX, C03DA, C03DB
Ischemic heart disease /angina	C01DA, C01DX16, C01EB15, C01EB17, C01EB18
Ischemic heart disease /hypertention	C07AA, C07AB, C07AG, C07BA, C07BB, C07BG, C07CA, C07CB, C07DA, C07DB, C07EA, C07EB, C07FA, C07FB, C08CA, C08CX, C08DA, C08DB, C08EA, C08EX, C08GA
Pain anti-inflamatory agents	M01A
Pain opiates	N02AA, N02AB, N02AC, N02AD, N02AF, 02AG N02AE01
Pancreatic insufficiencies	A09AA02
Rheumatic conditions	H02A, H02B, L04AB01, L04AB02, L04AB04, P01BA02
Renal disease	V03AE, A11CC, B03XA
Modified Rx-Risk-V Index based on (34; 43): continuous pharmaceutical innovation requires continuous Updating of ATC codes to identify comorbidities	