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Depression is associated with accelerated cognitive decline among patients with Type 2 diabetes in the ACCORD-MIND trial

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Abstract

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Context—Depression has been identified as a risk factor for dementia among patients with Type 2 diabetes mellitus but the cognitive domains and patient groups most affected have not been identified.

Objective—To determine whether comorbid depression in patients with type 2 diabetes accelerates cognitive decline.

Design—A 40-month cohort study of participants in the ACCORD-MIND trial

Setting—52 clinics organized into 6 clinical networks across the US and Canada.

Participants—2977 participants with Type 2 diabetes at high-risk for cardiovascular events

Main Outcome Measures—The Digit Symbol Substitution Test (DSST), Rey Auditory Verbal Learning Test (RAVLT), and the modified Stroop test were used to assess cognition. The Physician's Health Questionnaire-9 (PHQ-9) was used to assess depression. Mixed effects statistical models were used to analyze these cognitive outcomes incorporating depression as a time-dependent covariate.

Results—Participants with scores indicative of depression (PHQ-9 > 10) showed greater cognitive decline during 40-months follow-up on all tests, with the following differences in estimated least squares means: DSST 0.72 (95%CI 0.25, 1.19, p=0.0029), RAVLT 0.18 (95%CI 0.07, 0.29, p=0.0009), Stroop Interference −1.06 (95%CI −1.93, −0.18, p=0.0179). This effect of depression on risk of cognitive decline did not differ according to: previous cardiovascular disease, baseline cognition or age, intensive vs. standard treatment of glucose, blood pressure treatment, lipid treatment, or insulin use. Addition of demographic and clinical covariates to models did not significantly change the cognitive decline associated with depression.

Conclusions—Depression in patients with Type 2 diabetes was associated with greater cognitive decline in all domains, across all treatment arms, and in all participant subgroups assessed.

Depression and diabetes are among the most common illnesses in older primary care populations. Up to 20% of adult patients with type 2 diabetes meet criteria for comorbid major depression. Furthermore, each of these disorders is associated with an increased the risk of the other, with depression being associated with an increased risk of diabetes[1, 2] and adult-onset diabetes being associated with increased risk of subsequent depression[2].

Both depression and diabetes appear to be associated with an increased the risk of dementia. Lu and colleagues reviewed 16 studies and found that persons with diabetes had a 47% increased risk of all-cause dementia, a 39% increased risk of Alzheimer's disease (AD), and a 200% increased risk of vascular dementia compared to those without diabetes. Two recent systematic reviews found that depression was associated with a doubling[3] of the risk of subsequent AD and all-cause dementia in the general population of older adults.[4, 5] In the Cardiovascular Health Study population, this association between depression and incident mild cognitive impairment was independent of underlying vascular disease.[6]

Two recent studies in Health Maintenance Organization populations examined whether depression was associated with an increase in the risk of all-cause dementia among patients with diabetes. The first study among nearly 4,000 patients with type 2 diabetes found a

doubling of the risk of dementia diagnosis for patients with depression after 3–5 years of follow-up.[7] The second study of nearly 20,000 patients with Type 2 diabetes also found a doubling of the risk of a dementia diagnosis for patients with depression after 3–5 years of follow-up.[8] These studies were limited by their reliance on chart diagnoses of dementia which lack sensitivity and are prone to ascertainment bias. For example, clinicians often notice and diagnose only more severe cases of dementia.

The ACCORD-MIND study offers the opportunity to prospectively examine the effects of depression on cognitive decline in a well-characterized and well-managed cohort of participants prospectively assessed with a rigorous battery of cognitive tests. Our hypothesis was that depression (PHQ-9 ≥10) as a time-dependent co-variate would be associated with subsequent decline in cognitive function after controlling for relevant clinical variables.

METHODS

The ACCORD trial design is described elsewhere[9]. Briefly, ACCORD was a randomized, multicenter, double 2 × 2 factorial design trial of 10,251 middle-aged and older participants with Type 2 diabetes (T2D) who are at high risk for CVD events because of existing CVD (secondary prevention) or additional cardiovascular risk factors (primary prevention). All participants were enrolled into the glycemia trial, which compared a therapeutic strategy targeted to a glycated hemoglobin (HbA1c) level of <6.0% (intensive arm) to a strategy that targeted a glycated hemoglobin level of 7.0%–7.9% (standard arm). The lipid trial (54% of the total sample) compared the masked administration of either placebo or fenofibrate to persons taking simvastatin. The blood pressure trial included the other 46% of participants and compared a therapeutic strategy targeting a systolic blood pressure of <120 mmHg (intensive) to one targeting a systolic blood pressure of <140 mmHg (standard).

In February 2009, the intensive glycemic intervention was stopped because an increased risk for mortality was detected in that arm[10]. At that time all intensive glycemic control subjects were transitioned to the standard glycemic treatment, but MIND evaluations continued according to the original protocols. The lipid and blood pressure trials continued to the planned completion date in June, 2009.The trial was sponsored by the National Heart Lung and Blood Institute (NHLBI), and the protocol was approved by a review panel at the NHLBI as well as by the institutional review board or ethics committee at each center. The MIND sub-study was sponsored by the National Institute on Aging in collaboration with NHLBI, and was approved by the institutional review boards of all participating institutions (Appendix 1). Separate informed consent for MIND was signed by participants

The design of the MIND sub-study has been described previously[11]. Cognitive function was assessed with a test battery of cognitive functions typically affected in T2D[12] at baseline (targeted to be within 45 days of randomization), 20 months and 40 months after baseline. The choice of specific tests was based on several factors, including the distribution of the test score in non-demented adult populations, the ease of standardizing and monitoring the quality of test administration in multiple study sites, the time required to administer the test, and the frequency with which other studies have used the test.

Cognitive Function

The primary cognitive outcome for MIND was the number of correctly completed cells on the Digit Symbol Substitution Test (DSST), which is an omnibus test of psychomotor speed[13]. Secondary cognitive outcomes were verbal memory and executive function. Memory was measured with the Rey Auditory Verbal Learning Test (RAVLT),[14] and is reported as the average number of words recalled (0 to 15) over the immediate, short, and delayed recall trials. Higher scores on the DSST and RAVLT indicate better cognitive functioning. Executive functioning was measured with the modified Stroop test[15] and is reported as the interference score; a higher score is indicative of worse function. The Mini Mental State Examination was administered to allow comparison of the MIND sample with other samples, but it was not a study outcome due to its lack of sensitivity to cognitive decline. In addition to the cognitive tests, the Physician's Health Questionnaire-9[16] was administered to screen for depression, a frequent co-morbidity in T2D and potential confounder.

Participants were tested in a quiet setting during a scheduled ACCORD clinic visit. Before testing, capillary blood glucose level was measured and if <60 mg/dL, a snack was given to the participant, who then rested for 15 minutes before the battery was started. Quality control was monitored by the MIND Coordinating Center at the Roena B. Kulynych Center for Memory, Cognition Research, Department of Internal Medicine, Wake Forest University. To ensure quality control, we: 1) certified testers at baseline and semi-annually thereafter, 2) reviewed a 10% random sample of tape recordings acquired during testing, 3) did random reviews comparing test forms to data entered into the database, and 4) checked test and tester score distributions for unusual trends. Staff from the Coordinating Center was available throughout the study to answer testers' questions.

Depression assessment

Depressive symptoms were measured in ACCORD-MIND using the 9-item Patient Health Questionnaire (PHQ-9), the self-report version of the PRIME-MD, a well-validated psychiatric diagnostic interview for use in primary care settings.[17] A score of ≥10 on the PHQ-9 has been shown to have 77% sensitivity and 94% specificity to the diagnosis of major depression by structured psychiatric interview.[16] In patients with Type 2 diabetes, a PHQ-9 score of 10 or more has been associated with higher risk of mortality, dementia, as well as macrovascular and microvascular complications[18]. A recent review of the reliability and validity of depression screening tools in patients with diabetes, gave the PHQ-9 generally higher rates of sensitivity (66–100%), but lower rates of specificity (52–85%)[19].

Statistical Analyses

All statistical analyses were conducted at the ACCORD Coordinating Center, Wake Forest School of Medicine, with SAS 9.3 (SAS Institute, Cary, NC). Participant characteristics are summarized with means, standard deviations and percentages.

To test the effect of prior depression on change in cognitive function, we used a mixed effects regression model with unstructured covariance to model 20 month change in cognitive outcome by prior depression status (baseline depression for the 0–20 month

change; 20-month depression for the 20–40 month change). This model assumes the probability of missing outcomes depends only on previous recorded outcomes or factors in the model. For each cognitive outcome, we started with a basic model and added covariates to determine their effect on the relationship between depression and cognition. Model 1 (N=2777) adjusted for baseline age (years), female (y/n), race (white/non-white), education (four levels), glycemia group, BP vs Lipid Trial, BP group, Lipid group, and CCN (6-levels). Model 2 (N=2765) adjusted for all variables in Model 1, plus: prior CVD event (y/n), baseline BMI, baseline Hba1c, and baseline LDL-c. Model 3 (N= 2762) adjusted for all variables in Models 1 and 2, plus: current smoker at baseline (y/n) and alcohol use at baseline (0/>0). Model 4 (N=2762) adjusted for all variables in Models 1, 2, and 3, plus: any baseline insulin use (y/n). We did not adjust for baseline levels of cognition in our primary analyses because this has been shown to introduce bias when exposures are associated with baseline health status.[20–22] Analyses with adjustment for baseline cognition were conducted as a sensitivity analysis.

Using the adjustment factors from Model 4 for DSST, interactions between depression and previous CVD, age, intensive vs. standard treatment of glucose, blood pressure treatment, lipid treatment, and insulin treatment were tested. We also tested Model 4 using the PHQ-9 score as a continuous variable. As pre-specified, the main effect of depression on change in the cognitive primary outcome (DSST) was tested at the two-sided 0.05 significance level. All other hypothesis tests (interactions and analyses of secondary outcomes) were considered to be hypothesis generating and were also conducted at the 0.05 level. Since we present 12 tests of hypotheses each at the 0.05 level, there is a 46% chance (i.e. $1-[1-0.05]^{12}$) that at least one of these tests would be statistically significant at an alpha level of 0.05, assuming independence between tests.

Results

Study Participants

A total of 2977 participants were enrolled in the ACCORD-MIND substudy (Supplemental Table 1). Of these, 2764 completed the 20-month cognitive assessment and 2664 completed the 40-month cognitive assessment. Among participants, 531 (18%) scored 10 or greater on the PHQ-9 depression scale at baseline assessment. These participants scoring 10 or more were younger, more likely to be female and of non-Hispanic white ethnicity. They also had less education, were more likely to currently smoke cigarettes, but less likely to drink alcohol. They were more likely to have cardiovascular disease and heart failure and had a higher mean body mass index (BMI) and larger waist circumference. These participants also had higher baseline HbA1C, fasting glucose, LDL and total cholesterol. At baseline, participants scoring over 10 were more likely to be treated with insulin and beta-blockers, and less likely to be treated with sulfonylureas, metformin, ACE inhibitors, and aspirin. All other baseline measures were not statistically significant between depressed and non-depressed groups.

The proportion of participants scoring over 10 on the PHQ-9 decreased slightly over the course of the study (Table 1). There were 62% of participants with all three assessments who never had a PHQ-9 ≥10.5% had PHQ-9 ≥10 at all three assessments. 5% had PHQ-9

>10 at baseline but were < 10 at month 20 and month 40.28% had other patterns of PHQ scores or missing data.

Estimated least square means for decline in cognitive function during the 40 month follow-up were consistently greater for participants scoring 10 or more on the PHQ-9 at the prior assessment for all cognitive tests. (Tables 3–5). On the DSST (Table 2), a statistically significant difference was apparent (p=0.0029). Adjustment for progressively more extensive lists of demographic and clinical covariates (Models 1–4) did little to change the differences in means or statistical significance. On the RAVLT (Table 3), differences were approximately 0.2 units in all models (p=0.0009) in all models. On the Stroop test (Table 4), differences between groups were approximately −1.06 (p=0.0179) in all models. If PHQ-9 was entered into these models as a continuous variable, it remained significantly associated with cognitive decline on all 3 tests (DSST: β= −0.054 p= 0.004, RAVLT: β= −0.014, p= 0.001, STROOP: β= 0.079, p=0.023). A depression × insulin interaction term added to model 4 was not statistically significant for any of the cognitive outcomes. Similarly, interactions with previous CVD, baseline cognition or age, intensive vs. standard treatment of glucose, blood pressure treatment, and lipid treatment were not statistically significant.

Effects of depression on cognitive decline were larger and more statistically significant when the initial cognition level was included in the models for change (data not shown). Additional exploratory analyses revealed that subjects with PHQ-9 scores ≥ 10 at both baseline and 20-months showed the greatest cognitive decline on the DSST during both the 0–20 (mean decline −2.0 ± 7.4) and 20–40 (mean decline −2.7± 8.0) month intervals. The group with PHQ-9 <10 at baseline but ≥ 10 at 20 months showed nearly as large a decline (mean decline −2.5± 8.6) in the 20–40 month interval. Patients with PHQ-9 scores ≥ 10 at baseline were somewhat more likely to drop-out before the 40 month assessment (N=26), but omitting these individuals from the models did not significantly change the magnitude or significance of the changes noted. We have calculated a model R-squared value of 0.0249 using the method described by Edwards et al.[23]

Discussion

In a sample of participants with Type 2 diabetes for a mean of 9 years, depression was associated with accelerated decline on a battery of cognitive tests over 40 months of follow-up. Significant differences between depressed and non-depressed groups were found on the Digit-Symbol Substitution Test, the Rey Auditory Verbal Learning Test, and the Stroop test. RAVLT and Stroop did improve slightly over time in the non-depressed group, possibly due to a learning effect. This effect of depression on cognitive decline did not differ according to any of the factors examined: previous CVD, baseline cognition or age, intensive vs. standard treatment of glucose, blood pressure, and dyslipidemia, or insulin treatment. This is the clearest demonstration to date that depression constitutes a risk factor for cognitive decline in the population of patients with Type 2 diabetes. It also demonstrates that this effect is not limited to specific cognitive tests or specific subgroups. Further, the fact that the relationship was detectable during the 40-month duration of the study suggests this interaction between cognition and depression develops over relatively short time periods and needs to be monitored over time. The depression effect does not appear to be mediated by behaviors

leading to poor glucose, blood pressure or lipid control since all ACCORD-MIND participants received close follow-up and guideline concordant care.

Recent studies examining the risks associated with depressive symptoms in the population of patients with Type 2 diabetes utilized clinically recognized dementia rather than cognitive testing as the outcome of interest.[7, 8] These ICD-9 dementia diagnoses have been found to be specific (few false positives), but to have low sensitivity (many false negatives) for mild dementia. These retrospective studies are also prone to ascertainment bias. The cognitive testing protocol utilized in ACCORD-MIND is a more unbiased and sensitive outcome measure, allowing us to detect differences by depression status over a 40 month period as opposed to the 3–5 year period of these earlier studies. ACCORD-MIND also has very low rates of loss to follow-up which reduces the chances of the ascertainment bias that characterizes studies based on chart diagnoses. The ACCORD-MIND cognitive testing protocol also allowed us to demonstrate that depression accelerates decline in all cognitive domains assessed: psychomotor speed, verbal learning, and executive function. We were able to demonstrate that the effect of depression on cognitive decline was unaffected by: previous CVD, baseline cognition or age, intensive vs. standard treatment of glucose, blood pressure, and dyslipidemia, potentially depression-related health risk behaviors (BMI, smoking, alcohol use) or insulin treatment. We did not control for antidepressant treatment, because we did not have data on dose or duration of antidepressant treatment and did not have data on psychotherapy received.

It is difficult to comment on the clinical meaningfulness of these cognitive changes because we measured mean change and clinical meaningfulness is generally determined by whether a patient falls above or below an impairment threshold. However, the declines we observed can be compared to those noted in previous studies of cognitive decline in patients with diabetes. Over 40 months of follow-up in the MIND sample, non-depressed patients had a mean decline in unadjusted DSST scores of 1.7 points (0.51 points annual decline), while depressed patients declined 2.7 points (0.81 points annual decline). This compares to an approximately 0.49 points annual decline in the Atherosclerosis Risk in Communities Study (ARIC) sample mean aged 56.7 at baseline[24] and approximately 0.87 points annual decline in the Health, Aging, and Body Composition Study (HABC) sample of persons mean age 74.2 years with prevalent diabetes.[25] These studies did not compare declines by depression groups.

Most recent studies have demonstrated increased risk for dementia[26] and/or cognitive decline[27] in community dwelling older adults with depressive symptoms (usually elevated scores on CES-D). Some of the recent studies have shown elevated risk specifically in those with recurrent[28] or persistent[29] depressive symptoms. This is consistent with our exploratory analyses that showed the greatest cognitive decline in participants that score ≥ 10 on the PHQ-9 at both baseline and 20 months. There have been persistent questions about whether depression represents a risk factor for cognitive decline or whether depression represents an early manifestation of dementia. In our study, no patients had dementia at baseline and the effect of depression did not differ by baseline cognitive impairment, also suggesting that depression is not simply an early manifestation of dementia.

There are a number of mechanisms that might be responsible for the acceleration of cognitive decline in those ACCORD-MIND subjects who also had depression. In patients with diabetes, depression is associated with poor adherence to diet, exercise, smoking and medication recommendations[30], poor glycemic control[31], and an increased risk of microvascular and macrovascular complications[17, 32]. Each of these may contribute to the increased risk of dementia seen in patients with diabetes who are also depressed. Both depression and type 2 diabetes are also associated with signs of systemic inflammation[33, 34], decreased insulin sensitivity[34, 35], and autonomic dysfunction[36, 37], which may mediate the effects of depression on dementia risk. Studies of the increased risk for mortality and repeat cardiac events in patients with depression following myocardial infarction have suggested that most of this effect is due to health behavior, specifically physical activity and medication adherence.[38] In ACCORD, medication adherence was intensively monitored, but depression was associated with both increased BMI and waist circumference, so physical activity level might mediate the depression effect.

Depression has been associated with an array of biological abnormalities that may mediate the effect of depression on cognitive decline. Dysregulation of the hypothalamic-pituitary axis associated with depression results in greater glucocorticoid secretion and impaired negative feedback.[39–41] The resulting higher cortisol levels may damage brain areas involved in cognition such as the hypothalamus[42, 43] It may also decrease neurogenesis in brain areas essential for memory such as the hippocampus.[44–46] Depression has also been linked to increased proinflammatory factors, such as interleukin 6 and tumor necrosis factor.[47] Increases in cortisol and in proinflammatory factors are associated with insulin resistance, which has been identified as a risk factor for vascular dementia and AD.[4848]

There are a number of important limitations to the current study that should be noted. First, we lacked a control population of patients without diabetes and thus were unable to estimate the strength of the depression-cognitive decline association in non-diabetic patients. Second, there are a number of important differences in cardiovascular risk factors between depressed and non-depressed ACCORD-MIND participants that could account for the depression effect. We have attempted to control for these in our analyses. In general, these analyses showed little change in mean differences when these were added as covariates to our models. However, there may be residual confounding by these factors. Third, we used the PHQ-9 to assess depression. This is a self-report version of the PRIME-MD interview and does not yield a true depression diagnosis. Fourth, since this an observational study, we are not able to determine whether treatment of depression with pharmacotherapy or psychotherapy would reduce the risk of cognitive decline among similar patients with Type 2 diabetes. To address this question, it will be necessary to conduct a depression treatment randomized controlled trial among patients with diabetes and monitor cognitive outcomes.

In summary, this epidemiological analysis of the effect of depression on risk for cognitive decline among participants in the ACCORD-MIND study showed that depression is associated with cognitive decline in all domains assessed and that this effect does not differ in important clinical subgroups. This suggests that a potentially reversible factor may be promoting general cognitive decline in the broad population of patients with Type 2

diabetes. Since dementia is one of the fastest growing and most dreaded complications of diabetes, our findings may be important for public health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

MDS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1

ACCORD-MIND Participants with PHQ-9 score ≥ 10, by assessment time

		PHQ-9≥10	
Visit	**N**	**N**	**%**
Baseline	2977	531	18%
20 Months	2775	471	17%
40 Months	2648	415	16%
~Ever~	2977	878	29%

Table 2

Estimated Least Squares Means for Change in DSST by prior depression stat

	Prior Depression Group				
Outcome	**PHQ-9 < 10**	**PHQ-9 >= 10**	**Diff in Means**	**95% CI**	**p-value**
Model 1	−0.62 (−0.88, −0.37)	−1.36 (−1.81, −0.91)	0.74	(0.27, 1.20)	0.0020
Model 2	−0.61 (−0.87, −0.36)	−1.34 (−1.79, −0.88)	0.72	(0.25,1.19)	0.0027
Model 3	−0.62 (−0.88, −0.36)	−1.35 (−1.80, −0.90)	0.73	(0.26,1.20)	0.0025
Model 4	−0.61 (−0.87, −0.35)	−1.33 (−1.79, −0.88)	0.72	(0.25,1.19)	0.0029

Model 1: adjusted for baseline age (years), female (y/n), race (white,non-white), education (four levels), glycemia group, BP vs Lipid Trial, intensive vs standard BP, fenofibrate or placebo, and CCN

Model 2: adjusted for all variables in Model 1, plus: prior CVD event (yes/no), baseline BMI, baseline Hba1c, and baseline LDL

Model 3: adjusted for all variables in Models 1 and 2, plus: current smoker (y/n) at baseline, and alcohol use (0 vs >0) at baseline

Model 4: adjusted for all variables in Models 1, 2 and 3, plus: any baseline insulin use

Table 3

Estimated Least Squares Means for Change in RAVLT by prior depression status

	Prior Depression Group				
Outcome	**PHQ-9 < 10**	**PHQ-9 >= 10**	**Diff in Means**	**95% CI**	**p-value**
Model 1	0.25 (0.19,0.31)	0.07 (−0.03,0.17)	0.19	(0.08,0.29)	0.0006
Model 2	0.25 (0.19,0.31)	0.07 (−0.04,0.17)	0.18	(0.07,0.29)	0.0010
Model 3	0.25 (0.19,0.31)	0.07 (−0.04,0.17)	0.18	(0.07,0.29)	0.0010
Model 4	0.25 (0.19,0.31)	0.07 (−0.04,0.17)	0.18	(0.07,0.29)	0.0009

Model 1: adjusted for baseline age (years), female (y/n), race (white,non-white), education (four levels), glycemia group, BP vs Lipid Trial, intensive vs standard BP, fenofibrate or placebo, and CCN

Model 2: adjusted for all variables in Model 1, plus: prior CVD event (yes/no), baseline BMI, baseline Hba1c, and baseline LDL

Model 3: adjusted for all variables in Models 1 and 2, plus: current smoker (y/n) at baseline, and alcohol use (0 vs >0) at baseline

Model 4: adjusted for all variables in Models 1, 2 and 3, plus: any baseline insulin use

Table 4

Estimated Least Squares Means for Change in STROOP Interference Score by prior depression status

	Prior Depression Group				
Outcome	**PHQ-9 < 10**	**PHQ-9 >= 10**	**Diff in Means***	**95% CI**	**p-value**
Model 1	−0.89 (−1.38, −0.40)	0.18 (−0.66,1.03)	−1.07	(−1.95, −0.20)	0.0159
Model 2	−0.82 (−1.31, −0.34)	0.27 (−0.57,1.11)	−1.09	(−1.97, −0.22)	0.0141
Model 3	−0.84 (−1.33, −0.35)	0.20 (−0.64,1.05)	−1.04	(−1.92, −0.16)	0.0199
Model 4	−0.81 (−1.30, −0.32)	0.25 (−0.60,1.09)	−1.06	(−1.93, −0.18)	0.0179

*Reduction in scores is improvement on Stroop, so means favor non-depressed group

Model 1: adjusted for baseline age (years), female (y/n), race (white,non-white), education (four levels), glycemia group, BP vs Lipid Trial, intensive vs standard BP, fenofibrate or placebo, and CCN

Model 2: adjusted for all variables in Model 1, plus: prior CVD event (yes/no), baseline BMI, baseline Hba1c, and baseline LDL

Model 3: adjusted for all variables in Models 1 and 2, plus: current smoker (y/n) at baseline, and alcohol use (0 vs >0) at baseline

Model 4: adjusted for all variables in Models 1, 2 and 3, plus: any baseline insulin use