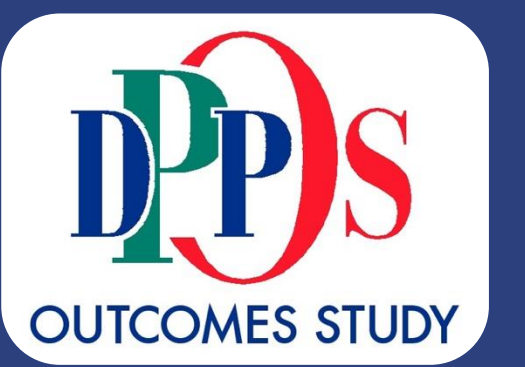


Association of Randomization to Metformin with Prevalent Cognitive Impairment Syndromes in the Diabetes Prevention Program Outcomes Study



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INTRODUCTION/OBJECTIVES

- Whether metformin affects dementia risk is unclear. Most of the human data are from non-randomized studies with administrative data.
- In the Diabetes Prevention Program (DPP) Outcomes Study (DPPOS), comprised of individuals with prediabetes and type 2 diabetes, we examined the association of randomized metformin (MET) vs placebo (PLB) and Intensive Lifestyle (ILS) interventions in the DPP with cognitive impairment (CI).

METHODS

- Participants (n=1483, mean age 74 ± 8.4) were evaluated for prevalent CI in 2022-2024.
- Randomization to MET, ILS or PLB (1996-1999) was followed by masked MET (1996-2001) and then open label MET in the original MET group until 2022.
- CI syndromes, ascertained using the National Alzheimer's Coordinating Center Uniform Dataset version 3 forms, included (in order of severity):
 - No CI
 - CI-not-Mild Cognitive Impairment (CI not MCI)
 - MCI (non-amnestic [naMCI] and amnestic [aMCI])
 - Dementia.
- We examined the association of randomization to MET with odds of CI syndromes using multinomial logistic regression.

RESULTS

- MET exposure was 15.5 ± 7.7 years per person in the MET group and out-of-study MET was 4.5 ± 5.1 person years in PLB and 3.8 ± 4.8 person years in ILS groups, largely for treating diabetes that developed during the study.
- Randomization to MET was associated with 59-62% and 60% lower odds of dementia compared with PLB and ILS, respectively (Table).

Table. Odds ratios (OR) and 95% confidence limits (CL) relating metformin randomization with CI.

	N		Metformin vs PLB			Metformin vs ILS		
			OR	95% CL	p	OR	95% CL	p
No CI	973	-	-	-	-	-	-	-
CI-not-MCI	189	M1*	1.25	(0.84, 1.87)	0.27	0.95	(0.65, 1.39)	0.79
		M2*	1.08	(0.70, 1.66)	0.73	1.04	(0.68, 1.59)	0.87
naMCI	136	M1	1.05	(0.67, 1.65)	0.82	1.11	(0.70, 1.77)	0.65
		M2	0.88	(0.53, 1.44)	0.61	0.94	(0.57, 1.55)	0.81
aMCI	137	M1	0.82	(0.52, 1.29)	0.39	1.17	(0.74, 1.84)	0.85
		M2	0.76	(0.46, 1.24)	0.27	1.04	(0.62, 1.75)	0.88
Dementia	48	M1	0.41	(0.18, 0.98)	0.04	0.40	(0.17, 0.92)	0.03
		M2	0.38	(0.15, 0.97)	0.04	0.40	(0.16, 1.02)	0.05

*Model 1 included age at CI assessment, sex, race/ethnicity, education, and income. Omnibus p = 0.34

*Model 2 also included APOE-4 genotype. Omnibus p = 0.31

When adjusted for multiple comparisons, the difference between MET and PLB was no longer significant.

DISCUSSION

- To the best of our knowledge, this is the first study to examine the association of randomization to metformin with cognitive impairment syndromes, ascertained using the Alzheimer's Disease Research Centers (ADRC) funded by the National Institute of Aging (NIA) in the United States.
- Our results suggest a threshold effect of metformin, delaying the transition from MCI to dementia.
- Examining this hypothesis requires further follow-up to examine cognitive transitions expecting a higher incidence of dementia as the population continues to age.

CONCLUSIONS

- Long-term exposure to metformin may prevent dementia among persons with pre-diabetes and type 2 diabetes.
- Longer follow-up with more dementia cases is needed to confirm our findings.

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