RESEARCH ARTICLE OPEN ACCESS

Association Between Regular Laxative Use and Incident Dementia in UK Biobank Participants

Zhirong Yang, PhD,* Chang Wei, MSc,* Xiaojuan Li, PhD, Jinqiu Yuan, PhD, Xuefeng Gao, PhD, Bingyu Li, PhD, Ziyi Zhao, MPH, Sengwee Toh, ScD, Xin Yu, MD, Carol Brayne, MD, Zuyao Yang, PhD, Feng Sha, PhD, and Jinling Tang, PhD

Neurology® 2023;100:e1702-e1711. doi:10.1212/WNL.0000000000207081

Correspondence
Dr. Sha
feng.sha@siat.ac.cn
or Dr. Yang
zyang@cuhk.edu.hk

Abstract

Background and Objectives

The use of over-the-counter laxatives is common in the general population. The microbiome-gut-brain axis hypothesis suggests that the use of laxatives could be associated with dementia. We aimed to examine the association between the regular use of laxatives and the incidence of dementia in UK Biobank participants.

Methods

This prospective cohort study was based on UK Biobank participants aged 40–69 years without a history of dementia. Regular use of laxatives was defined as self-reported use in most days of the week for the last 4 weeks at baseline (2006–2010). The outcomes were all-cause dementia, Alzheimer disease (AD), and vascular dementia (VD), identified from linked hospital admissions or death registers (up to 2019). Sociodemographic characteristics, lifestyle factors, medical conditions, family history, and regular medication use were adjusted for in the multivariable Cox regression analyses.

Results

Among the 502,229 participants with a mean age of 56.5 (SD 8.1) years at baseline, 273,251 (54.4%) were female, and 18,235 (3.6%) reported regular use of laxatives. Over a mean follow-up of 9.8 years, 218 (1.3%) participants with regular use of laxatives and 1,969 (0.4%) with no regular use developed all-cause dementia. Multivariable analyses showed that regular use of laxatives was associated with increased risk of all-cause dementia (hazard ratio [HR] 1.51; 95% CI 1.30–1.75) and VD (HR 1.65; 95% CI 1.21–2.27), with no significant association observed for AD (HR 1.05; 95% CI 0.79–1.40). The risk of both all-cause dementia and VD increased with the number of regularly used laxative types (p trend 0.001 and 0.04, respectively). Among the participants who clearly reported that they were using just 1 type of laxative (n = 5,800), only those using osmotic laxatives showed a statistically significantly higher risk of all-cause dementia (HR 1.64; 95% CI 1.20–2.24) and VD (HR 1.97; 95% CI 1.04–3.75). These results remained robust in various subgroup and sensitivity analyses.

Discussion

Regular use of laxatives was associated with a higher risk of all-cause dementia, particularly in those who used multiple laxative types or osmotic laxative.

*These authors contributed equally to this work as first authors.

From the Shenzhen Institute of Advanced Technology (Zhirong Yang, C.W., Z.Z., F.S., J.T.), Chinese Academy of Sciences, Guangdong, China; Primary Care Unit (Zhirong Yang), School of Clinical Medicine, University of Cambridge, United Kingdom; Department of Population Medicine (X.L., S.T.), Harvard Medical School & Harvard Pilgrim Health Care Institute, Boston, MA; Center for Digestive Disease (J.Y.), The Seventh Affiliated Hospital, Sun Yat-sen University; Central Laboratory (X.G.), Shenzhen Key Laboratory of Precision Medicine for Hematological Malignancies, Shenzhen University General Hospital; School of Government (B.L.), Shenzhen University, Guangdong; Peking University Sixth Hospital (X.Y.), Peking University Institute of Mental Health, Beijing, China; Cambridge Public Health (C.B.), School of Clinical Medicine, University of Cambridge, United Kingdom; Division of Epidemiology (Zuyao Yang, J.T.), The JC School of Public Health & Primary Care, The Chinese University of Hong Kong; and Clinical Data Center (J.T.), Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangdong, China.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by Shenzhen Science and Technology Program (Grant No. KQTD20190929172835662).

Glossary

AD = Alzheimer disease; **aHR** = adjusted HR; **BNF** = British National Formulary; **HR** = hazard ratio; **MgO** = magnesium oxide; **OTC** = over the counter; **PD** = Parkinson disease; **SES** = socioeconomic status; **SMD** = standardized mean difference; **TMAO** = trimethylamine N-oxide; **VD** = vascular dementia.

As a major cause of disability and dependency of older adults, dementia is one of the greatest global challenges for health and social care. The number of people living with dementia was estimated to be over 43.8 million worldwide in 2016 and is expected to rise exponentially to 152 million by 2050.[1] With only 40% of dementia cases attributable to established modifiable risk factors, further identification of preventable risk factors has become a crucial priority for alleviating the global burden of dementia.[2]

Constipation affects 20% of the general population,[3] 40% of community-dwelling older adults, and 70% of nursing home residents.[4,5] With an increasing trend in the use of laxatives,[6-8] the Compound Annual Growth Rate of the global laxatives market is projected to rise by 5.5% from 2020 to 2028, starting from US$ 5.5 billion in 2019.[9] In the United Kingdom, about 85% of people with constipation were treated with laxatives.[10] Current British guidance recommends starting with bulk-forming laxatives or fecal softeners for constipation, and if the condition persists, adding or switching to osmotic or stimulant laxatives.[11] As all laxatives are available over the counter (OTC), laxative abuse is common among middle-aged and older adults, especially those who take multiple medicines that may induce constipation or those who believe that daily bowel movements are necessary for good health (e.g., for weight loss).[12] These individuals usually begin using laxatives when constipation first occurs and develop a habit of using them afterward.[12] Stimulant laxatives, which have the most immediate effect, are the most frequent choice in laxative abuse.[12]

Use of laxatives can lead to a new steady state of gut microbiota composition and long-term changes in the adaptive immune response.[13] Recent research has also suggested that gut dysbiosis can affect the modulation of nerve signaling and the production of numerous neurotransmitters (such as acetylcholine, serotonin, dopamine, and gamma-aminobutyric acid) for normal cognitive function.[14] Disruptions of gut microbiota composition may also increase the production of intestinal toxins, such as lipopolysaccharides, which have been associated with amyloid deposition, regional inflammatory response, and neural damage in animal studies.[14,15] These multiple pathways in the microbiome-gut-brain axis[16] support a hypothesis that regular use of laxatives may be associated with the risk of dementia.

However, few population studies have investigated this association directly. A recent cohort study showed that magnesium oxide (MgO), a common type of osmotic laxatives, was associated with a lower risk of dementia.[17] However, the small sample size and lack of comparisons between different types of laxatives in that study have limited its value in assessing the roles of laxatives in the development of dementia. To comprehensively examine whether the use and different types of laxatives are associated with the risk of dementia, we conducted a large population-based cohort study using data from the UK Biobank.

Methods

Data Source and Study Population

Data were from the UK Biobank, with nearly 500,000 volunteering participants aged 40–69 years across England, Wales, and Scotland recruited between 2006 and 2010. At baseline visit, data on demographics, lifestyle, and health status were collected at assessment centers through touchscreen questionnaires, verbal interviews, and physical measurements. Health-related outcomes are available through linked records from primary care, hospital inpatient, death, and cancer registers. All participants who had not been diagnosed with dementia by the time of recruitment were included in this study. The UK Biobank received ethical approval from the research ethics committee (REC reference for UK Biobank 11/NW/0382), and participants provided written informed consent.

Exposures

The primary exposure of interest was self-reported regular use of any type of laxatives in the touchscreen questionnaire and verbal interview at baseline. Participants were asked whether they were regularly taking specific common OTC treatments including medications for constipation. Regular use was defined as most days of the week for the last 4 weeks in the questionnaire. If a participant reported any regular medication intake, the names of the medication were recorded if available. Four main subtypes of laxatives for regular users, fecal softeners, bulk-forming laxatives, osmotic laxatives, and stimulant laxatives as defined by the British National Formulary (BNF), were analyzed.[11]

Outcomes

We used algorithmically defined health-related outcomes preprocessed by the UK Biobank, in which all-cause dementia and subtypes of dementia were ascertained through linkage to data from primary care, hospital admissions, and death registers during follow-up.[18] Follow-up started from recruitment and ended at the time of incident dementia, death, loss to follow-up, or latest data update (March 2019), whichever occurred first. The primary outcome of interest was all-cause dementia. Two of its subtypes, namely Alzheimer disease (AD) and vascular dementia (VD), were examined as secondary outcomes. Other types of dementia were not analyzed separately in this study

due to rare occurrence or unclear classification of dementia in the UK Biobank. The accuracy of using routinely collected health care data sets to identify incident dementia is high in terms of positive predictive value (80%–92%), sensitivity (78%), and specificity (92.0%–96.6%), whereas the positive predictive value is relatively low for subtype diagnoses (71% for AD and 44% for VD).[19,20]

Covariates

Based on previous reviews,[21-23] 4 groups of baseline covariates were considered in our adjustment models: (1) sociodemographics (age, sex, ethnicity [White vs non-White], education level [university degree or higher vs others], and socioeconomic status [SES]), (2) lifestyle factors (smoking status [never, former vs current smoking], alcohol consumption [never or occasionally drinking, ≤14 units of alcohol per week vs >14 units per week], dietary consumption of vegetables, fruit, fish [≥twice a week vs <twice a week], and processed/unprocessed meat [≤once a week vs >once a week], physical activities [moderate, high vs low, categorized according to World Health Organization recommendations],[24] and body mass index), (3) medical conditions and family history (diabetes, heart attack, stroke, high blood pressure, Parkinson disease [PD], depression, cognitive function, and parental history of dementia), and (4) regular medication use (opioids, anticholinergic drugs, statins, steroids, calcium channel blockers, and antidiarrheal agents). SES was measured by Townsend Deprivation Index categorized into 5 quintiles. One serving of vegetable or fruit consumption was defined according to the recommendation in a comprehensive review.[25] Medical conditions were self-reported except PD (defined by algorithm) and cognitive function (tested via reaction time). Anticholinergic drugs were defined according to a previous study,[26] and other medications were defined based on BNF.[11] Other variables were determined through baseline touchscreen questionnaires or algorithmically defined data if available. More descriptions about covariates are in eTable 1 (links.lww.com/WNL/C645).

Main Analysis

Baseline characteristics were presented as frequency (percentage) for categorical variables and mean (SD) for continuous variables. The standardized mean difference (SMD) was used to denote the magnitude of imbalance in baseline characteristics by regular use of laxatives and by missing data status. An absolute value of SMD greater than 0.1 indicated meaningful imbalance.[27] Cox proportional hazards models with age as the time scale[28] were used to estimate the hazard ratio (HR) and 95% CI for the association between regular laxative use and the risk of incident dementia (all-cause dementia, AD, and VD individually). The proportional hazards assumption was tested by visual inspection using Schoenfeld residuals.

Four sets of models with progressive adjustment for potential confounders were conducted: model 1 adjusted for sociodemographic variables, model 2 additionally adjusted for lifestyle factors, model 3 additionally adjusted for medical conditions and family history, and model 4 additionally adjusted for regular use of other medications. The fully adjusted Cox proportional hazards model (model 4) was used to examine the association between regular use of laxatives and the risk of incident dementia. Using model 4, we further performed subgroup analysis by age (<65 and ≥65 years), sex, SES (below and above median), ethnicity (White and non-White), and education levels (university degree or higher and below university degree).

STATA 16 statistical software was used for all analyses. The results from complete-case analyses, which excluded the participants with missing data of covariates, were presented as the main results.

Secondary Analysis

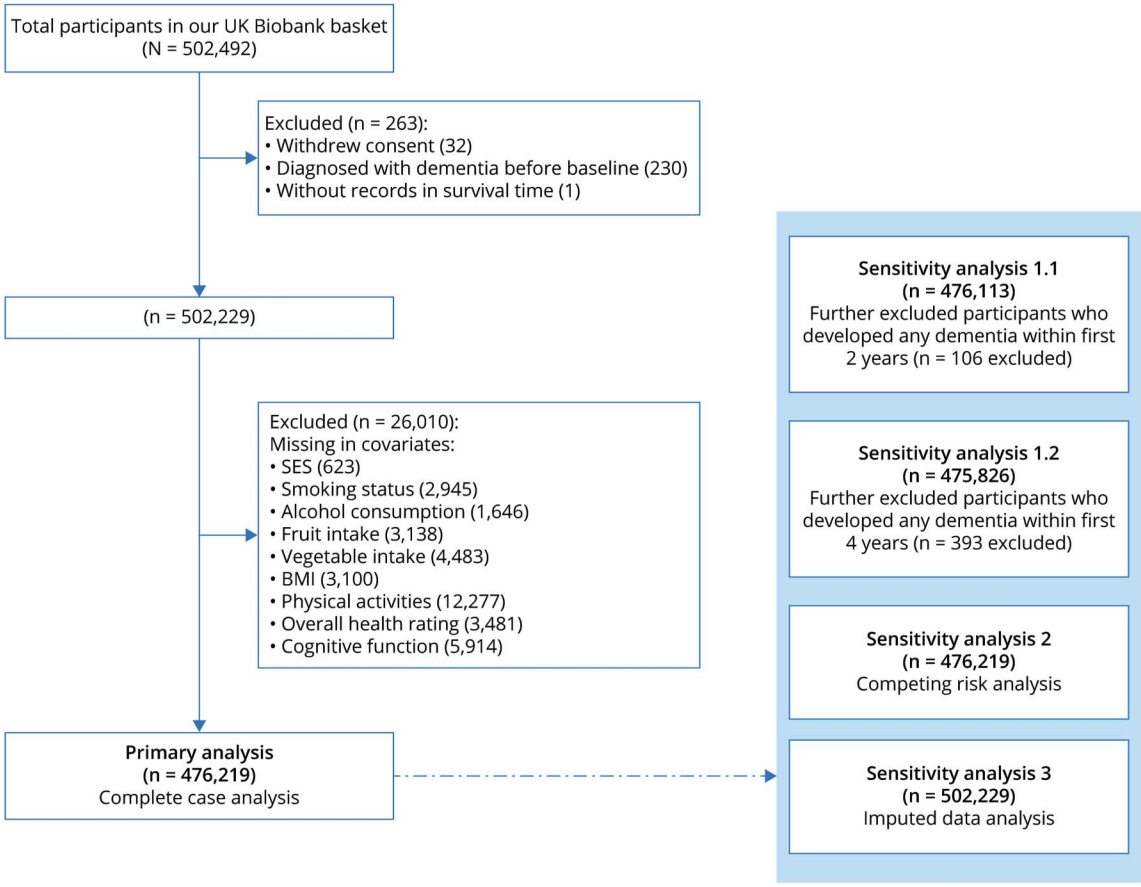
As regular use of laxatives is a proxy of chronic constipation, it is possible that the association between laxatives and dementia, if present, was attributable to, at least partly, the association between constipation and dementia. To examine this possibility, a direct comparison among different types of laxatives was conducted in the participants who were taking laxatives (all of them should have constipation and thus were more comparable in this regard) and reported the specific types of laxatives. This issue was not examined by restricting to people with constipation or adjusting for constipation in Cox regression models because the status of constipation was known for only tens of participants and inclusion of constipation and use of laxatives simultaneously in 1 model would lead to multicollinearity.

Another 3 sets of sensitivity analyses were also conducted. First, to rule out the possibility of reversal causality between regular use of laxatives and dementia, participants who developed any dementia within the first 2 years or 4 years were excluded in separate analyses. Second, to examine the potential effect of missing data, multiple imputations were conducted for missing data in covariates.[29] Third, to eliminate the influence induced by death before potential dementia occurrence, Fine and Gray competing-risks regression models were used to calculate the subdistribution HR by treating death as a competing-risks event. Moreover, we categorized the outcome as early-onset dementia (diagnosis before age 65 years) and late-onset dementia (diagnosis after 65 years) and tested the associations of regular laxative use with early-onset dementia among the participants aged 65 years or less and late-onset dementia among the all the participants with early-onset dementia as censor.

Negative Control Outcome Analysis

A negative control outcome analysis was conducted to examine whether the association between laxative use and dementia in our main analysis could be due to residual confounding.[30] Hip fracture was selected as the negative control outcome given that a similar set of confounders is shared by the relationships of laxative use with hip fracture and dementia, such as frailty and time-varying conditions, which were not fully captured in our study. According to relevant trials and observational research,[31,32] hip fracture was expected not to be associated with laxative use in our analysis, and otherwise, it may indicate that the association of

Figure 1 Flowchart of the Study



BMI = body mass index; SES = socioeconomic status.

laxative use with dementia would be distorted by residual confounding.[30] Hip fracture was identified using data from hospital inpatient admissions. People diagnosed with hip fracture before baseline assessment were further excluded from this analysis. An association between laxative use and hip fracture would suggest residual confounding in our main findings.

Data Availability

Data are available from the UK Biobank after submitting an application (ukbiobank.ac.uk/register-apply/). The syntax for conducting the analysis is available on request.

Results

Baseline Characteristics

We identified 502,229 eligible participants (Figure 1), 18,235 (3.6%) of whom reported regular use of laxatives at baseline visit. Laxative users were more likely to be women, have a higher SES, have a lower education degree, have a long-standing illness, and regularly take anticholinergic and opioid drugs (Table 1). They were also more likely to have less alcohol consumption, more weekly fruit consumption, and less processed meat consumption. The prevalence of stroke, high blood pressure, depression, poor overall self-health rating, and the uptake of calcium channel blockers, statins, and steroid drugs were higher in regular than nonregular users. Participants with missing baseline data tended to be non-White, have more comorbidities, and have more medications (eTable 2, links.lww.com/WNL/C645).

Laxative Use and Dementia

Among 476,219 participants with complete baseline data, a total of 2,187 cases of all-cause dementia (including 824 AD and 450 VD) were recorded over a mean follow-up of 9.8 (SD 1.5) years. The mean age at all-cause dementia diagnosis was 67.1 (SD 8.1), 68.8 (SD 7.9), and 67.0 (SD 8.1) years for all participants, regular users of laxatives, and nonregular users, respectively. Compared with the nonregular use, the fully adjusted HR (aHR) for the association with regular laxative use was 1.51 (95% CI 1.30–1.75) for all-cause dementia, 1.65 (95% CI 1.21–2.27) for VD, and 1.05 (95% CI 0.79–1.40) for AD (Table 2).

Among 16,703 regular laxative users, 6,530 participants reported specific types of laxatives they were taking (5,800 participants used only 1 type of laxative, and 730 used 2 or more). The risk of all-cause dementia increased with the number of laxative types, with an aHR of 1.28 (95% CI

Table 1 Baseline Characteristics of the Study Population

Characteristics	Total	Regular laxative use, n (%)		SMD[a]
		Yes	No	
No. of participants	502,229	18,235 (3.6)	483,994 (96.4)	
Baseline age, y, mean (SD)	56.5 (8.1)	58.4 (7.8)	56.5 (8.1)	0.25
Women	273,251 (54.4)	13,809 (75.7)	259,442 (53.6)	0.48
Non-White	27,017 (5.4)	1,255 (6.9)	25,762 (5.3)	0.07
University degree or higher	234,905 (46.8)	6,807 (37.3)	228,098 (47.1)	0.20
Socioeconomic status				0.13
Low	100,607 (20.1)	3,196 (17.5)	97,411 (20.2)	
Intermediate	300,702 (59.9)	10,348 (56.8)	290,354 (60.1)	
High	100,297 (20.0)	4,668 (25.6)	95,629 (19.8)	
Smoking status				0.02
Never	273,384 (54.8)	9,163 (50.6)	264,221 (54.9)	
Former	172,949 (34.6)	6,772 (37.4)	166,177 (34.5)	
Current	52,951 (10.6)	2,189 (12.1)	50,762 (10.5)	
Alcohol consumption				0.32
Never or occasionally	98,565 (19.7)	5,702 (31.4)	92,863 (19.3)	
Monthly or weekly ≤14 units	176,809 (35.3)	6,605 (36.3)	170,204 (35.3)	
Weekly >14 units	225,209 (45.0)	5,877 (32.3)	219,332 (45.5)	
Living alone	92,858 (18.5)	4,005 (22.0)	88,853 (18.4)	0.09
Vegetable consumption (servings), mean (SD)	4.9 (3.4)	5.1 (3.5)	4.9 (3.4)	0.05
Fruit consumption (servings), mean (SD)	3.1 (2.6)	3.5 (3.0)	3.1 (2.6)	0.15
Fish consumption ≥twice a week	259,955 (51.8)	9.698 (53.2)	250,257 (51.7)	0.03
Processed meat consumption ≤once a week	345,012 (68.7)	13,496 (74.0)	331,516 (68.5)	0.12
Unprocessed red meat consumption ≤once a week	341,201 (67.9)	12,601 (69.1)	328,600 (67.9)	0.03
Physical activities				0.04
Low	207,775 (42.4)	8,238 (47.1)	199,537 (42.2)	
Moderate	124,399 (25.4)	4,299 (24.6)	120,100 (25.4)	
High	157,778 (32.2)	4,952 (28.3)	152,826 (32.3)	
Cognitive function (reaction time), mean (SD)	559.6 (117.9)	588.6 (136.2)	558.3 (116.8)	0.24
Diabetes	26,057 (5.2)	1,374 (7.5)	24,683 (5.1)	0.10
Heart attack	11,588 (2.3)	697 (3.8)	10,891 (2.3)	0.09
Stroke	7,647 (1.5)	615 (3.4)	7,032 (1.5)	0.13
High blood pressure	135,662 (27.0)	6,228 (34.2)	129,434 (26.7)	0.16
Parkinson disease	936 (0.2)	158 (0.9)	778 (0.2)	0.10
Inflammatory bowel disease	4,227 (0.8)	202 (1.1)	4,025 (0.8)	0.03
Body mass index, mean (SD)	27.4 (4.8)	27.8 (5.3)	27.4 (4.8)	0.06
Depression	15,980 (3.2)	1,365 (7.5)	14,615 (3.0)	0.20
Family history of dementia	58,308 (11.6)	2,328 (12.8)	55,980 (11.6)	0.04

Continued

Table 1 Baseline Characteristics of the Study Population *(continued)*

Characteristics	Total	Regular laxative use, n (%)		SMD[a]
		Yes	No	
Overall health rating				0.55
Excellent	81,842 (16.4)	1,315 (7.3)	80,527 (16.8)	
Good	288,913 (57.9)	8,288 (45.8)	280,625 (58.4)	
Fair	105,274 (21.1)	5,689 (31.5)	99,585 (20.7)	
Poor	22,719 (4.6)	2,786 (15.4)	19,933 (4.1)	
Long-standing illness, disability, or infirmity	159,704 (31.8)	9,799 (53.7)	149,905 (31.0)	0.47
Anticholinergic drugs	21,846 (4.3)	2,990 (16.4)	18,856 (3.9)	0.42
Calcium channel blocker drugs	30,973 (6.2)	1,631 (8.9)	29,342 (6.1)	0.11
Opioids	15,355 (3.1)	2,028 (11.1)	13,327 (2.8)	0.33
Statins	79,463 (15.8)	4,165 (22.8)	75,298 (15.6)	0.19
Antidiarrheal agents	383 (0.1)	23 (0.1)	360 (0.1)	0.02
Steroids	19,044 (3.8)	1,397 (7.7)	17,647 (3.6)	0.18

The numbers in the parenthesis are column percentages, unless stated otherwise.
[a] SMD is the standardized mean difference shown as an absolute value, which indicates meaningful imbalance if its value is greater than 0.1.

1.03–1.61) for use of single laxative type and 1.90 (95% CI 1.20–3.01) for combination use of 2 or more laxative types (p trend = 0.001, Table 3). In the comparison of each laxative type to the reference group, only osmotic laxative was found to be associated with a higher risk of all-cause dementia (aHR 1.64, 95% CI 1.20–2.24, Table 4). When these 2 analyses were performed for each type of dementia separately, the 95% CIs became much wider, and many point estimates were odd probably because of the much fewer outcome events. Despite so, the results for VD showed consistent trends to those for all-cause dementia, that is, the risk of VD increased with the number of laxative types (p trend = 0.04, Table 3) and was associated with osmotic laxative only (aHR 1.97; 95% CI 1.04–3.75, Table 4). Subgroup analyses showed that the associations between laxative use and the risk of dementia did not vary appreciably with age, sex, SES, ethnicity, and education (eFigures 1 and 2, links.lww.com/WNL/C645). Moreover, the association between laxative use and dementia did not vary considerably with a history of stroke and regular use of opioids, which indicated that the association between laxatives and dementia was not influenced by these factors (eFigures 1 and 2).

Sensitivity Analyses

When the comparison of different types of laxatives was restricted to participants who were taking laxatives regularly, using bulk-forming laxatives as the reference group, osmotic laxative was still significantly associated with all-cause dementia (aHR 2.10, 95% CI 1.20–3.69, eTable 3, links.lww.com/WNL/C645), indicating that the observed association between laxatives and dementia did not just

Table 2 Association Between Regular Laxative Use and Risk of All-Cause Dementia, Alzheimer Disease, and Vascular Dementia

Outcome	Regular laxative use		Hazard ratio (95% CI)			
	Yes (n = 16,703)	No (n = 459,516)	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
All-cause dementia	218 (1.3)	1,969 (0.4)	2.52 (2.19–2.90)***	2.36 (2.05–2.72)***	1.59 (1.37–1.84)***	1.51 (1.30–1.75)***
Alzheimer disease	55 (0.3)	769 (0.2)	1.54 (1.17–2.03)***	1.45 (1.10–1.91)***	1.11 (0.83–1.46)	1.05 (0.79–1.40)
Vascular dementia	47 (0.3)	403 (0.1)	2.73 (2.01–3.70)***	2.48 (1.82–3.37)***	1.74 (1.27–2.37)***	1.65 (1.21–2.27)***

Participants with baseline missing values (n = 26,010) were excluded from modeling analysis.
*p < 0.05, **p < 0.01, and ***p < 0.001.
[a] Adjusted for sociodemographic variables: age (time scale), sex, ethnicity, education, and socioeconomic status.
[b] Additionally adjusted for lifestyle factors: smoking status, alcohol consumption, living alone, dietary consumption of vegetable, fruit, fish, and processed/unprocessed meat, physical activities, and body mass index.
[c] Additionally adjusted for medical conditions: diabetes, heart attack, stroke, high blood pressure, Parkinson disease, inflammatory bowel disease, depression, cognitive test, family history of dementia, overall health rating, and long-standing illness.
[d] Additionally adjusted for status of regular medication use: opioids, anticholinergic drugs, statins, calcium channel blockers, antidiarrheal agents, and steroids.

Table 3 Association of Number of Laxative Types Used With the Risk of Dementia

	All-cause dementia			Alzheimer disease			Vascular dementia		
No. of laxative types	Cases/total	HR (95% CI)	*p* for trend	Cases/total	HR (95% CI)	*p* for trend	Cases/total	HR (95% CI)	*p* for trend
No regular use	1,969/459,516 (0.4)	1 (ref)	0.001	769/459,516 (0.2)	1 (ref)	0.38	403/459,516 (0.1)	1 (ref)	0.04
Single type	87/5,800 (1.5)	1.28 (1.03–1.61)*		18/5,800 (0.3)	0.77 (0.48–1.24)		18/5,800 (0.3)	1.31 (0.81–2.13)	
2 or more types	19/730 (2.6)	1.90 (1.20–3.01)**		9/730 (1.2)	2.39 (1.22–4.68)*		5/730 (0.7)	2.43 (0.99–5.97)	
Unspecified	112/10,173 (1.1)	1.66 (1.37–2.02)***	—	28/10,173 (0.3)	1.11 (0.76–1.63)	—	24/10,173 (0.2)	1.86 (1.23–2.83)**	—

Abbreviation: HR = hazard ratio.
Models are fully adjusted for sociodemographic variables, lifestyle factors, medical conditions, and status of regular medication use.
Among 730 participants taking 2 or more classes of laxatives, different combinations of laxative classes are bulk-forming and softening (19 participants), bulk-forming and stimulant (105), bulk-forming and osmotic (173), softening and stimulant (66), softening and osmotic (44), stimulant and osmotic (270), softening, stimulant, and osmotic (21), bulk-forming, stimulant, and osmotic (19), bulk-forming, softening, and osmotic (3), and bulk-forming, softening, and stimulant (10). Unspecified types of laxatives were not considered when assessing the linear trend.
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

reflect the association, if any, between constipation and dementia. Other sensitivity analyses also yielded similar findings to the main analyses, except that the association between laxative use and VD was attenuated when excluding participants diagnosed with all-cause dementia within the first 4 years of their follow-up (aHR 1.35; 95% CI 0.93–1.97, eTables 3–7). We also tested the associations of regular laxative use with early-onset dementia among the participants aged 65 years or less and late-onset dementia among all the participants with early-onset dementia as censor. Their associations with laxative use were similar (eTables 8 and 9).

Negative Control Outcome Analysis

In the negative control outcome analysis using the fully adjusted model, no significant difference was found for overall regular use (aHR 1.05; 95% CI 0.87–1.28, eTable 10, links.lww.com/WNL/C645), making it less likely that the observed associations between regular use of laxatives and all-cause dementia and VD were caused by residual confounding.

Discussion

In this 10-year follow-up study of 502,229 UK Biobank participants, we found that regular use of laxatives was associated with a higher risk of all-cause dementia and VD. For both outcomes, the risk increased with the number of regularly used laxative types and was more pronouncedly associated with osmotic laxative. Negative control outcome analysis and various sensitivity analyses suggested that the associations were not substantially influenced by confounding or reversal causality.

It might be speculated that the stronger association observed between osmotic laxative and dementia was caused, at least

Table 4 Association of Regular Use of Specific Types of Laxatives With Risk of All-Cause Dementia, Alzheimer Disease, and Vascular Dementia

	All-cause dementia		Alzheimer disease		Vascular dementia	
Laxative class	Cases/total	HR (95% CI)	Cases/total	HR (95% CI)	Cases/total	HR (95% CI)
No regular use	1,969/459,516 (0.4)	1 (ref)	769/459,516 (0.2)	1 (ref)	403/459,516 (0.1)	1 (ref)
Bulk-forming	19/2,339 (0.8)	0.86 (0.54–1.35)	5/2,339 (0.2)	0.59 (0.24–1.42)	5/2,339 (0.2)	1.13 (0.46–2.74)
Softening	6/315 (1.9)	1.25 (0.56–2.80)	1/315 (0.3)	0.60 (0.08–4.31)	2/315 (0.6)	1.47 (0.36–6.05)
Osmotic	44/2,051 (2.1)	1.64 (1.20–2.24)**	7/2,051 (0.3)	0.81 (0.38–1.72)	10/2,051 (0.5)	1.97 (1.04–3.75)*
Stimulant	18/1,095 (1.6)	1.28 (0.80–2.05)	5/1,095 (0.5)	1.05 (0.43–2.55)	1/1,095 (0.1)	0.34 (0.05–2.44)

Abbreviation: HR = hazard ratio.
This analysis included 459,516 participants with no regular use of laxatives and 5,800 participants who reported the use of single type of laxatives. Models are fully adjusted for sociodemographic variables, lifestyle factors, medical conditions, and status of regular medication use.
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

partly, by the association between constipation severity and dementia. Indeed, previous studies found a higher prevalence of constipation (19.2%) among patients with dementia in a cross-sectional study,[33] and constipation was associated with dementia among patients with PD.[34,35] However, according to the current British guidelines,[11] osmotic laxative is recommended for mild to moderate constipation when fecal softener or bulk-forming laxative does not work, and stimulant laxatives are recommended for more severe constipation. If different types of laxatives would have just been a proxy for constipation severity, stimulant laxatives should have shown a stronger association with dementia than osmotic laxatives and others, which is not the case in this study. Therefore, the association between osmotic laxatives and dementia would be more likely to reflect the potential effects of the type of laxatives per se.

Although the exact mechanisms linking laxatives with dementia have yet to be investigated, 1 possible explanation is that laxatives can influence gut microbiome composition and cognitive function in the microbiome-gut-brain axis.[16] A laboratory study showed lasting influence of an osmotic laxative on gut microbiome composition.[13] The alteration to the gut microbiota may affect the production of numerous neurotransmitters for normal cognitive function and increase the production of intestinal toxins that associated with the inflammatory response.[14] Laxatives may also disrupt the intestinal epithelial barrier and facilitate passage of gut microbial–derived neurotoxic metabolites into the CNS.[36] Some microorganisms may then reach the brain in conditions of decreased barrier integrity,[14] for example, in stroke, which has been recognized as a known risk factor for dementia, especially VD.[37,38] Indeed, gut bacteria dysbiosis caused by laxatives could increase production of trimethylamine N-oxide (TMAO) and its entry to the blood.[39] High plasma TMAO levels lead to platelet hyperactivity, thrombosis, vascular inflammation, and atherosclerosis that contribute to the pathology of stroke and VD.[14,40,41] Moreover, despite the greater genetic contributions to risk of early-onset dementia, the above mechanism may apply to both early-onset and late-onset dementia.

Previous evidence in this regard was limited, with only 1 relevant study published to date. That study included 1,547 MgO users and 4,641 nonusers. Opposite to our findings, it found that use of this specific osmotic laxative was associated with lower risk of dementia (aHR 0.52; 95% CI 0.41–0.79).[17] The study was based on insurance claims data, with MgO use defined as an incident MgO prescription. Unlike self-reported regular use in our study, an incident prescription of MgO is not necessarily equivalent to a regular intake of MgO. Moreover, the study only controlled for age, sex, and comorbidity, whereas our study further adjusted for other known important confounders (e.g., education, socioeconomic factors, and use of other medications) to reduce the impact of confounding.

This study investigated the association between laxative use and dementia, with a large study population, long-term follow-up, and control for potential confounders. However, there are several limitations that should be borne in mind when interpreting our findings. First, volunteer selection bias may exist in our study because the response rate at baseline in the UK Biobank was only 5.5%.[42] However, many associations observed in other studies could be replicated in the UK Biobank,[43] suggesting that selection bias, if existent in this study, is not greater than that in others. Second, as dementia in the UK Biobank was ascertained through linkage to the participants' health-related records, underrecording might have occurred. If underrecording occurred more in participants with no regular use of laxative due to fewer contact with health services (these participants seemed healthier in our study population), the association observed in this study would tend to be overestimated. However, subgroup analyses by long-standing illness and overall health rating (both of which related to the frequency of contact with health services) showed similar results across subgroups, which did not support that detection bias was a major problem in this study. In addition, the accuracy of diagnosis of dementia subtypes, AD and VD, is relatively lower in the UK Biobank. Thus, further studies on the association between laxatives use and dementia subtype are warranted. Third, as laxatives are OTC medications, it is not feasible to validate the self-report use of laxatives using medical records as a standard reference. However, a previous study found that self-reported medication use showed high validity in the general population in Scotland when compared with national prescribing data.[44] In addition, because of unspecified types of laxatives and low incidence of dementia, this study could be insufficiently powered to investigate the associations between other types of laxatives than osmotic and dementia. Fourth, we could not adjust for time-varying confounding in our study given a limited number of people providing information on time-varying variables, which was a common problem of most cohort studies. If the status of laxative use of some participants switched overtime (from regular use to no use or the inverse), the association between laxatives and dementia observed in this study might have been underestimated because long-term uninterrupted use would putatively be even more strongly associated with the outcome. Fifth, data on potential confounders, such as dietary fiber intake, severity of constipation, and personal preference for taking laxatives (e.g., side effects, cost, and availability), were limited in the UK Biobank and thus not controlled in our analysis, which may lead to residual confounding. Sixth, we could not explicitly explore the dose-response relation between laxative use and risk of dementia, as dosage information was not available in the UK Biobank.

Previous studies mainly focused on short-term adverse events of laxatives.[45] The findings of this study suggested that regular use of laxatives, even without short-term severe adverse events, may have the potential long-term risk of dementia, especially when it comes to osmotic laxatives and combination use of 2 or more types of laxatives. In fact, osmotic and stimulant laxatives are both not recommended for regular use, yet we still found many regular users of these medications in

this study. Many patients with constipation may misuse laxatives because they tend to self-treat with OTC medications. Therefore, pharmacists and clinicians should be well placed in providing instructions for patients regarding the use of OTC medications for treating constipation. If the long-term side effect of laxatives on cognition is confirmed, medical professionals should also convey this information to stakeholders to reduce the risk of dementia due to misuse or overuse of laxatives. Instead of regular use of laxatives, constipation can be mitigated most of the time by lifestyle changes, such as increasing fluid intake, dietary fiber, and activity levels, which may also benefit brain health.[46-48]

Our main finding is the discovery of the association for the first time. Therefore, this finding requires confirmation by further studies before more actions should be taken. To give better estimates of the association for each laxative type, future studies on this topic should try to collect more accurate data on the types of laxatives and dementia and conduct more powerful analysis of the association for each laxative type. More studies are also needed to identify potential contributory factors or specific mechanisms that may be responsible for the observed associations in our study. If regular laxative use has a true causative association with dementia risk, future studies on the associations of laxatives with other chronic diseases, such as stroke, depression, and PD, which may insidiously develop through similar mechanisms in terms of inflammation and alternation of gut microbiota, are warranted.

In conclusion, regular use of laxatives was associated with a higher risk of all-cause dementia. This risk increased with the number of regularly used laxative types and was more pronouncedly associated with osmotic laxative. Further studies are needed to clarify whether the association between laxatives and dementia observed in our study is causal.

Acknowledgment

The authors thank the UK Biobank participants. This research has been conducted using the UK Biobank resource under application number 80476.

Study Funding

This work was supported by the National Natural Science Foundation of China (grant no. 72274193), the Shenzhen Science and Technology Program (grant no. KQTD20190929172835662), and the Strategic Priority Research Program of Chinese Academy of Sciences (grant no. XDB 38040200).

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* September 14, 2022. Accepted in final form January 6, 2023. Submitted and externally peer reviewed. The handling editor was Associate Editor Linda Hershey, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Zhirong Yang, PhD	Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Guangdong, China; Primary Care Unit, School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design
Chang Wei, MSc	Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Xiaojuan Li, PhD	Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content
Jinqiu Yuan, PhD	Center for Digestive Disease, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content
Xuefeng Gao, PhD	Central Laboratory, Shenzhen Key Laboratory of Precision Medicine for Hematological Malignancies, Shenzhen University General Hospital, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content
Bingyu Li, PhD	School of Government, Shenzhen University, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content
Ziyi Zhao, MPH	Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content
Sengwee Toh, ScD	Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content
Xin Yu, MD	Peking University Sixth Hospital, Peking University Institute of Mental Health, Beijing, China	Drafting/revision of the manuscript for content, including medical writing for content
Carol Brayne, MD	Cambridge Public Health, School of Clinical Medicine, University of Cambridge, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content
Zuyao Yang, PhD	Division of Epidemiology, The JC School of Public Health & Primary Care, The Chinese University of Hong Kong, China	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design
Feng Sha, PhD	Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content, and study concept or design

Appendix *(continued)*

Name	Location	Contribution
Jinling Tang, PhD	Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Guangdong; Division of Epidemiology, The JC School of Public Health & Primary Care, The Chinese University of Hong Kong; Clinical Data Center, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangdong, China	Drafting/revision of the manuscript for content, including medical writing for content

References

1. WHO. *Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines*. WHO; 2019.
2. WHO. *Dementia: A Public Health Priority*. WHO; 2012. Accessed August 1, 2021. who.int/publications/i/item/dementia-a-public-health-priority.
3. Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol*. 2004;99(4):750-759. doi:10.1111/j.1572-0241.2004.04114.x.
4. Koloski NA, Jones M, Wai R, et al. Impact of persistent constipation on health-related quality of life and mortality in older community-dwelling women. *Am J Gastroenterol*. 2013;108(7):1152-1158. doi:10.1038/ajg.2013.137.
5. Fosnes GS, Lydersen S, Farup PG. Drugs and constipation in elderly in nursing homes: what is the relation? *Gastroenterol Res Pract*. 2012;2012:290231. doi:10.1155/2012/290231.
6. Gustafsson M, Lamas K, Isaksson U, et al. Constipation and laxative use among people living in nursing homes in 2007 and 2013. *BMC Geriatr*. 2019;19(1):38. doi:10.1186/s12877-019-1054-x.
7. Gage H, Goodman C, Davies SL, et al. Laxative use in care homes. *J Adv Nurs*. 2010;66(6):1266-1272. doi:10.1111/j.1365-2648.2010.05297.x.
8. Hosia-Randell H, Suominen M, Muurinen S, et al. Use of laxatives among older nursing home residents in Helsinki, Finland. *Drugs Aging*. 2007;24(2):147-154. doi:10.2165/00002512-200724020-00006.
9. Acute Market Reports. *Laxatives Market Size, Market Share, Application Analysis, Regional Outlook, Growth Trends, Key Players, Competitive Strategies and Forecasts, 2020 to 2028*. Acute Market Reports; 2020.
10. Shafe AC, Lee S, Dalrymple JS, et al. The LUCK study: laxative usage in patients with GP-diagnosed constipation in the UK, within the general population and in pregnancy. An epidemiological study using the General Practice Research Database (GPRD). *Therap Adv Gastroenterol*. 2011;4(6):343-363. doi:10.1177/1756283X11417483.
11. Joint Formulary Committee. *BNF 80: September 2020-March 2021*. Pharmaceutical Press; 2020.
12. Roerig JL, Steffen KJ, Mitchell JE, et al. Laxative abuse. *Drugs*. 2010;70(12):1487-1503. doi:10.2165/11898640-000000000-00000.
13. Tropini C, Moss EL, Merrill BD, et al. Transient osmotic perturbation causes long-term alteration to the gut microbiota. *Cell*. 2018;173(7):1742-1754 e17. doi:10.1016/j.cell.2018.05.008.
14. Luc M, Misiak B, Pawlowski M, et al. Gut microbiota in dementia. Critical review of novel findings and their potential application. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;104:110039. doi:10.1016/j.pnpbp.2020.110039.
15. Lukiw WJ, Li W, Bond T, et al. Facilitation of gastrointestinal (GI) tract microbiome-derived lipopolysaccharide (LPS) entry into human neurons by amyloid beta-42 (Abeta42) peptide. *Front Cell Neurosci*. 2019;13:545. doi:10.3389/fncel.2019.00545.
16. Alkasir R, Li J, Li X, et al. Human gut microbiota: the links with dementia development. *Protein Cell*. 2017;8(2):90-102. doi:10.1007/s13238-016-0338-6.
17. Tzeng NS, Chung CH, Lin FH, et al. Magnesium oxide use and reduced risk of dementia: a retrospective, nationwide cohort study in Taiwan. *Curr Med Res Opin*. 2018;34(1):163-169. doi:10.1080/03007995.2017.1385449.
18. UK Biobank Outcome Adjudication Group. *Definitions of Dementia and the Major Diagnostic Pathologies, UK Biobank Phase 1 Outcomes Adjudication*. UK Biobank; 2018.
19. Wilkinson T, Schnier C, Bush K, et al. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. *Eur J Epidemiol*. 2019;34(6):557-565. doi:10.1007/s10654-019-00499-1.
20. Sommerlad A, Perera G, Singh-Manoux A, et al. Accuracy of general hospital dementia diagnoses in England: sensitivity, specificity, and predictors of diagnostic accuracy 2008-2016. *Alzheimers Dement*. 2018;14(7):933-943. doi:10.1016/j.jalz.2018.02.012.
21. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6.
22. Yu JT, Xu W, Tan CC, et al. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J Neurol Neurosurg Psychiatry*. 2020;91(11):1201-1209. doi:10.1136/jnnp-2019-321913.
23. Peters R, Booth A, Rockwood K, et al. Combining modifiable risk factors and risk of dementia: a systematic review and meta-analysis. *BMJ Open*. 2019;9(1):e022846. doi:10.1136/bmjopen-2018-022846.
24. World Health Organization. *WHO Guidelines on Physical Activity and Sedentary Behaviour*. WHO; 2020:viii, 93 p. The Basque version is published by the Basque Government's Physical Activity and Sports Office. The Thai version is published by is the Ministry of Health in Thailand.
25. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. *Circulation*. 2016;133(2):187-225. doi:10.1161/circulationaha.115.018585.
26. Gray SL, Hanlon JT. Anticholinergic medication use and dementia: latest evidence and clinical implications. *Ther Adv Drug Saf*. 2016;7(5):217-224. doi:10.1177/2042098616658399.
27. Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *BMJ*. 2005;330(7497):960-962. doi:10.1136/bmj.330.7497.960.
28. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol*. 1997;145(1):72-80. doi:10.1093/oxfordjournals.aje.a009034.
29. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med*. 2009;28(15):1982-1998. doi:10.1002/sim.3618.
30. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;21(3):383-388. doi:10.1097/EDE.0b013e3181d61eeb.
31. Vijayvargiya P, Camilleri M, Vijayvargiya P, et al. Systematic review with meta-analysis: efficacy and safety of treatments for opioid-induced constipation. *Aliment Pharmacol Ther*. 2020;52(1):37-53. doi:10.1111/apt.15791.
32. Haring B, Pettinger M, Bea JW, et al. Laxative use and incident falls, fractures and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *BMC Geriatr*. 2013;13:38. doi:10.1186/1471-2318-13-38.
33. Wang F, Fei M, Hu WZ, et al. Prevalence of constipation in elderly and its association with dementia and mild cognitive impairment: a cross-sectional study. *Front Neurosci*. 2021;15:821654. doi:10.3389/fnins.2021.821654.
34. Camacho M, Macleod A, Maple-Grødem J, et al. Early constipation predicts faster dementia onset in Parkinson's disease. *NPJ Parkinsons Dis*. 2021;7(1):45.
35. Leta V, Urso D, Batzu L, et al. Constipation is associated with development of cognitive impairment in de novo Parkinson's disease: a longitudinal analysis of two international cohorts. *J Parkinsons Dis*. 2021;11(3):1209-1219. doi:10.3233/JPD-212570.
36. Sochocka M, Donskow-Łysoniewska K, Diniz BS, et al. The gut microbiome alterations and inflammation-driven pathogenesis of Alzheimer's disease: a critical review. *Mol Neurobiol*. 2019;56(3):1841-1851. doi:10.1007/s12035-018-1188-4.
37. Kubota Y, Iso H, Tamakoshi A. Bowel movement frequency, laxative use, and mortality from coronary heart disease and stroke among Japanese men and women: the Japan Collaborative Cohort (JACC) study. *J Epidemiol*. 2016;26(5):242-248. doi:10.2188/jea.JE20150123.
38. Sumida K, Molnar MZ, Potukuchi PK, et al. Constipation and risk of death and cardiovascular events. *Atherosclerosis*. 2019;281:114-120. doi:10.1016/j.atherosclerosis.2018.12.021.
39. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19(5):576-585. doi:10.1038/nm.3145.
40. Zhang J, Wang L, Cai J, et al. Gut microbial metabolite TMAO portends prognosis in acute ischemic stroke. *J Neuroimmunol*. 2021;354:577526. doi:10.1016/j.jneuroim.2021.577526.
41. Zhu W, Gregory JC, Org E, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell*. 2016;165(1):111-124. doi:10.1016/j.cell.2016.02.011.
42. Allen N, Sudlow C, Downey P, et al. UK Biobank: current status and what it means for epidemiology. *Health Policy Technol*. 2012;1(3):123-126. doi:10.1016/j.hlpt.2012.07.003.
43. Batty GD, Gale CR, Kivimäki M, et al. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ*. 2020;368:m131. doi:10.1136/bmj.m131.
44. Hafferty JD, Campbell AI, Navrady LB, et al. Self-reported medication use validated through record linkage to national prescribing data. *J Clin Epidemiol*. 2018;94:132-142. doi:10.1016/j.jclinepi.2017.10.013.
45. Rao SSC, Brenner DM. Efficacy and safety of over-the-counter therapies for chronic constipation: an updated systematic review. *Am J Gastroenterol*. 2021;116(6):1156-1181. doi:10.14309/ajg.0000000000001222.
46. Jiang X, Huang J, Song D, et al. Increased consumption of fruit and vegetables is related to a reduced risk of cognitive impairment and dementia: meta-analysis. *Front Aging Neurosci*. 2017;9:18. doi:10.3389/fnagi.2017.00018.
47. de Souto Barreto P, Demougeot L, Vellas B, et al. Exercise training for preventing dementia, mild cognitive impairment, and clinically meaningful cognitive decline: a systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci*. 2018;73(11):1504-1511. doi:10.1093/gerona/glx234.
48. Lauriola M, Mangiacotti A, D'Onofrio G, et al. Neurocognitive disorders and dehydration in older patients: clinical experience supports the hydromolecular hypothesis of dementia. *Nutrients*. 2018;10(5):562. doi:10.3390/nu10050562.

Association Between Regular Laxative Use and Incident Dementia in UK Biobank Participants

Zhirong Yang, Chang Wei, Xiaojuan Li, et al.

Neurology 2023;100;e1702-e1711 Published Online before print February 22, 2023
DOI 10.1212/WNL.0000000000207081