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Article

The associations of diuretics and laxatives use with cardiovascular mortality. An individual patient-data meta-analysis of two large cohort studies

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Table S1. Use of antihypertensive drug classes at baseline in the ESTHER study and the UK Biobank

Drug class	ESTHER (n = 4,253)		UK BIOBANK (n = 105,359)	
	n	(%)	n	(%)
Diuretics	897	(21.1)	38,227	(36.3)
β-blockers	2,095	(49.3)	32,193	(30.6)
Calcium channel blockers	1,168	(27.5)	33,463	(31.7)
Angiotensin-converting enzyme inhibitors	1,660	(39.0)	46,001	(43.7)
Angiotensin receptor blockers	513	(12.1)	19,963	(19.0)

UK, United Kingdom.

Table S2. Baseline characteristics of laxative users compared to non-users of laxatives of the analyzed participants with antihypertensive treatment in the ESTHER study and the UK Biobank

Laxative use	ESTHER (n = 4,253)			UK BIOBANK (n = 105,359)		
	Yes (n = 345)	No (n = 3,908)		Yes (n = 4,322)	No (n = 101,037)	
Characteristics	n [%]	n [%]	p-value	n [%]	n [%]	p-value
Age $\geq$ 65 years	57.1	46.8	< 0.001	41.6	36.0	< 0.001
Sex (male)	25.8	46.8	< 0.001	32.3	53.8	< 0.001
Smoking			0.181			< 0.001
Never	54.8	51.5		46.1	48.1	
Former	30.4	35.3		42.6	43.1	
Current	14.9	13.2		11.4	8.8	
Vigorous physical activity ^a			0.218			< 0.001
No	61.1	57.6		57.5	45.3	
Yes	39.0	42.4		42.6	54.7	
Alcohol consumption ^b			< 0.001			< 0.001
Abstainer	48.0	35.3		22.5	11.7	
WHO category I	47.3	58.6		57.3	63.0	
WHO category II/III	4.7	6.1		20.2	25.3	
SBP (mmHg)			0.176			< 0.001
< 140	34.3	32.4		44.2	35.9	
140 to < 160	44.3	41.6		36.4	39.6	
$\geq$ 160	21.4	26.0		19.4	24.6	
BMI (kg/m ²)			0.060			< 0.001
< 25	20.6	17.9		20.8	17.9	
25 to < 30	40.9	47.5		38.2	42.6	
$\geq$ 30	38.6	34.6		41.0	39.6	
Urinary albumin (mg /L)			0.575			0.615
< 20	79.5	78.2		66.9	66.3	
$\geq$ 20	20.5	21.8		33.2	33.8	
Diabetes mellitus	26.3	22.2	0.080	10.9	10.8	0.788
Heart failure ^c	25.4	17.1	< 0.001	N.A.	N.A.	N.A.
CHD	25.5	22.0	0.129	21.3	16.6	< 0.001
History of MI	12.6	10.0	0.138	9.6	8.9	0.130
History of stroke	8.9	5.2	0.005	3.9	2.8	< 0.001
Anticholinergic drug use	9.0	4.9	0.001	18.5	6.3	< 0.001
Opioid use	2.0	0.7	0.010	26.1	8.4	< 0.001
Diuretics use	29.6	20.3	< 0.001	43.6	36.0	< 0.001
Non-potassium-sparing diuretics	15.4	10.3	0.004	39.3	33.8	< 0.001
Potassium-sparing diuretics or combinations ^d	14.2	10.1	0.016	4.3	2.2	< 0.001

Bold printed: statistically significant ($p < 0.05$).

^a Vigorous physical activity was measured in hours per week (ESTHER study) and in number of days per week of at least 10 min of activity (UK Biobank): “No”: Participants not doing any amount of vigorous physical activity, “Yes”: Participants doing any amount of vigorous physical activity.

^b Alcohol consumption in categories of the WHO: Category I including women with an alcohol consumption of 0-19.99 g/day or men with 0-39.99 g/day, category II including women with an alcohol consumption of 20-39.99 g/day or men with 40-59.99 g/day, and category III including women with an alcohol consumption of ≥ 40 g/day or men with ≥ 60 g/day.

^c Not sufficiently assessed in the UK Biobank (unreliable self-report) and therefore not applicable for use.

^d Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

BMI, Body Mass Index; *CHD*, Coronary heart disease; *MI*, Myocardial infarction; *N.A.*, Not applicable; *SBP*, Systolic blood pressure; *SD*, Standard deviation; *UK*, United Kingdom; *WHO*, World health organization.

Table S3. Baseline characteristics of diuretics users compared to non-users of diuretics of the analyzed participants with antihypertensive treatment in the ESTHER study and the UK Biobank

Diuretics use	ESTHER (n = 4,253)			UK BIOBANK (n = 105,359)		
	Yes (n = 897)	No (n = 3,356)		Yes (n = 38,227)	No (n = 67,132)	
Characteristics	n [%]	n [%]	p-value	n [%]	n [%]	p-value
Age $\geq$ 65 years	56.6	45.2	< 0.001	38.9	34.8	< 0.001
Sex (male)	40.5	46.3	0.002	42.7	58.7	< 0.001
Smoking			0.251			< 0.001
Never	54.0	51.2		49.2	47.4	
Former	34.0	35.1		42.2	43.6	
Current	12.1	13.7		8.6	9.0	
Vigorous physical activity ^a			0.094			< 0.001
No	60.4	57.3		48.7	44.2	
Yes	39.6	42.8		51.4	55.8	
Alcohol consumption ^b			< 0.001			< 0.001
Abstainer	42.6	34.7		13.6	11.4	
WHO category I	53.7	58.8		61.2	63.6	
WHO category II/III	3.7	6.5		25.2	25.0	
SBP (mmHg)			0.797			< 0.001
< 140	33.4	32.3		34.9	36.9	
140 to < 160	41.0	42.1		40.2	39.0	
$\geq$ 160	25.6	25.6		25.0	24.1	
BMI (kg/m ²)			< 0.001			< 0.001
< 25	12.7	19.6		15.1	19.6	
25 to < 30	40.9	48.6		39.5	44.0	
$\geq$ 30	46.4	31.8		45.4	36.4	
Urinary albumin (mg /L)			0.007			< 0.001
< 20	75.0	79.2		67.4	65.7	
$\geq$ 20	25.1	20.8		32.6	34.3	
Diabetes mellitus	30.9	20.3	< 0.001	10.2	11.2	< 0.001
Heart failure ^c	28.5	15.0	< 0.001	N.A.	N.A.	N.A.
CHD	31.2	19.9	< 0.001	11.0	20.1	< 0.001
History of MI	15.4	8.9	< 0.001	5.8	10.7	< 0.001
History of stroke	8.2	4.7	< 0.001	3.2	2.6	< 0.001
Anticholinergic drug use	5.5	5.2	0.768	7.4	6.5	< 0.001
Opioid use	1.6	0.6	0.006	11.1	8.0	< 0.001
Laxative use	11.4	7.2	< 0.001	4.9	3.6	< 0.001

Bold printed: statistically significant ($p < 0.05$)

^a Vigorous physical activity was measured in hours per week (ESTHER study) and in number of days per week of at least 10 min of activity (UK Biobank): “No”: Participants not doing any amount of vigorous physical activity, “Yes”: Participants doing any amount of vigorous physical activity.

^b Alcohol consumption in categories of the WHO: Category I including women with an alcohol consumption of 0-19.99 g/day or men with 0-39.99 g/day, category II including women with an alcohol consumption of 20-39.99 g/day or men with 40-59.99 g/day, and category III including women with an alcohol consumption of ≥ 40 g/day or men with ≥ 60 g/day.

^c Not sufficiently assessed in the UK Biobank (unreliable self-report) and therefore not applicable for use.

BMI, Body Mass Index; *CHD*, Coronary heart disease; *MI*, Myocardial infarction; *N.A.*, Not applicable; *SBP*, Systolic blood pressure; *SD*, Standard deviation; *UK*, United Kingdom; *WHO*, World health organization.

Table S4. Baseline characteristics of users of non-potassium-sparing diuretics compared to users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics of the analyzed participants with antihypertensive treatment in the ESTHER study and the UK Biobank

Users of	ESTHER (n = 4,253)			UK BIOBANK (n = 105,359)		
	Non-potassium-sparing diuretics (n = 455)	Potassium-sparing diuretics or diuretics combinations ^a (n = 442)		Non-potassium-sparing diuretics (n = 35,821)	Potassium-sparing diuretics or diuretics combinations ^a (n = 2,406)	
Characteristics	n [%]	n [%]	p-value	n [%]	n [%]	p-value
Age ≥ 65 years	58.2	55.0	0.324	38.8	40.4	0.112
Sex (male)	43.7	37.1	0.043	42.8	41.0	0.074
Smoking			0.054			< 0.001
Never	52.6	55.4		49.5	45.6	
Former	37.2	30.6		42.1	43.9	
Current	10.1	14.0		8.5	10.5	
Vigorous physical activity ^b			0.976			< 0.001
No	60.3	60.4		47.9	59.4	
Yes	39.7	39.6		52.1	40.6	
Alcohol consumption ^c			0.880			< 0.001
Abstainer	41.7	43.4		13.1	20.9	
WHO category I	54.5	53.0		61.5	56.5	
WHO category II/III	3.8	3.6		25.4	22.7	
SBP (mmHg)			0.013			< 0.001
< 140	29.0	38.0		33.8	51.0	
140 to < 160	42.7	39.2		40.6	33.2	
≥ 160	28.3	22.8		25.6	15.8	
BMI (kg/m ²)			0.479			< 0.001
< 25	12.1	13.4		15.1	15.7	
25 to < 30	39.6	42.3		39.8	34.5	
≥ 30	48.4	44.3		45.1	49.9	

Users of	ESTHER (n = 4,253)			UK BIOBANK (n = 105,359)		
	Non-potassium-sparing diuretics (n = 455)	Potassium-sparing diuretics or diuretics combinations ^a (n = 442)		Non-potassium-sparing diuretics (n = 35,821)	Potassium-sparing diuretics or diuretics combinations ^a (n = 2,406)	
Characteristics	n [%]	n [%]	p-value	n [%]	n [%]	p-value
Urinary albumin (mg /L)			0.002			0.124
< 20	70.4	79.6		67.6	65.1	
≥ 20	29.6	20.4		32.4	34.9	
Diabetes mellitus	35.3	26.3	0.004	10.0	12.7	< 0.001
Heart failure ^d	31.5	25.4	0.046	N.A.	N.A.	N.A.
CHD	35.2	27.2	0.010	10.1	24.0	< 0.001
History of MI	17.2	13.4	0.119	5.1	15.5	< 0.001
History of stroke	9.0	7.4	0.393	3.2	3.5	0.305
Anticholinergic drug use	4.8	6.1	0.401	7.2	10.6	< 0.001
Opioid use	1.3	1.8	0.553	10.7	17.1	< 0.001
Laxative use	11.7	11.1	0.791	4.7	7.8	< 0.001

Bold printed: statistically significant ($p < 0.05$).

^a Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

^b Vigorous physical activity was measured in hours per week (ESTHER study) and in number of days per week of at least 10 min of activity (UK Biobank): “No”: Participants not doing any amount of vigorous physical activity, “Yes”: Participants doing any amount of vigorous physical activity.

^c Alcohol consumption in categories of the WHO: Category I including women with an alcohol consumption of 0-19.99 g/day or men with 0-39.99 g/day, category II including women with an alcohol consumption of 20-39.99 g/day or men with 40-59.99 g/day, and category III including women with an alcohol consumption of ≥ 40 g/day or men with ≥ 60 g/day.

^d Not sufficiently assessed in the UK Biobank (unreliable self-report) and therefore not applicable for use.

BMI, Body Mass Index; *CHD*, Coronary heart disease; *MI*, Myocardial infarction; *N.A.*, Not applicable; *SBP*, Systolic blood pressure; *UK*, United Kingdom; *WHO*, World Health Organization.

Table S5. Associations with CVM in users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics compared to non-users of diuretics in the UK Biobank

Drug class	UK BIOBANK		
	(n = 105,359; 1,616 cases)		
	n ^a	n _{cases} ^b	HR (95%CI) ^c
Non-users of diuretics	67,132	887	Ref.
Users of potassium-sparing diuretics	490	26	2.76 (1.87; 4.07)
Users of non-potassium-sparing diuretics combined with potassium-sparing diuretics	1,675	101	3.15 (2.56; 3.87)
Users of non-potassium-sparing diuretics combined with potassium	241	5	1.51 (0.63; 3.62)

Bold printed: statistically significant ($p < 0.05$).

^a Sample sizes exemplarily taken from imputed data set no. 1.

^b Case numbers do not add up to the total study case number (n=1,616) due to 597 cases within the users of non-potassium-sparing diuretics (not shown).

^c Adjusted for age, sex, smoking status, physical activity, alcohol consumption, systolic blood pressure, body mass index, potential kidney damage (urinary albumin ≥ 20 mg/L), diabetes mellitus, coronary heart disease, history of myocardial infarction, history of stroke, anticholinergic drug use, and use of opioids.

CI, Confidence interval; CVM, Cardiovascular mortality; HR, Hazard ratio; Ref., Reference; UK, United Kingdom.

Table S6. Associations with CVM comparing users and non-users of laxatives, diuretics overall, and diuretics in specific in the ESTHER study using only the first 7 years of follow-up or the complete follow-up of 14 years

Drug class	ESTHER (7 years of FUP) (n = 4,253; 169 cases)			ESTHER (14 years of FUP) (n = 4,253; 476 cases)		
	n ^a	n _{cases}	HR (95%CI) ^b	n ^a	n _{cases}	HR (95%CI) ^b
Laxatives						
Non-users	3,890	153	Ref.	3,890	433	Ref.
Users	363	16	1.09 (0.64; 1.87)	363	43	0.99 (0.70; 1.41)
Diuretics overall						
Non-users	3,356	109	Ref.	3,356	327	Ref.
Users	897	60	1.45 (1.06; 2.06)	897	149	1.39 (1.13; 1.70)
Diuretics in specific						
Non-users	3,356	109	Ref.	3,356	327	Ref.
Users of non-potassium-sparing diuretics	455	40	1.75 (1.21; 2.53)	455	90	1.49 (1.17; 1.89)
Users of potassium-sparing diuretics or combinations ^c	442	20	0.96 (0.59; 1.54)	442	59	1.10 (0.83; 1.46)

Bold printed: statistically significant ($p < 0.05$).

^a Sample sizes exemplarily taken from imputed data set no. 1.

^b Adjusted for age, sex, smoking status, physical activity, alcohol consumption, systolic blood pressure, body mass index, potential kidney damage (urinary albumin ≥ 20 mg/L), diabetes mellitus, heart failure, coronary heart disease, history of myocardial infarction, history of stroke, anticholinergic drug use, and use of opioids.

^c Group comprises users of potassium-sparing diuretics / combinations of non-potassium-sparing diuretics with potassium or potassium-sparing diuretics.

CI, Confidence interval; CVM, Cardiovascular mortality; FUP, Follow-up; HR, Hazard ratio; Ref.; Reference.