

Association of Tumor Necrosis Factor- α Inhibitors with Incident Dementia

Analysis based on Population-Based Cohort Studies

Submission to: Drugs & Aging

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Supplement Table 1. ATC- and ICD- codes

Generic drug name	ATC codes
Anti-inflammatory biologicals/biosimilars	
<i>TNFi</i>	
Adalimumab	L04AA17 (2005-2007) L04AB04 (2008-)
Certolizumab pegol	L04AB05 (2008-)
Etanercept	L04AA11 (2005-2007) L04AB01 (2008-)
Golimumab	L04AB06 (2010-)
Infliximab	L04AA12 (2005-2007) L04AB02 (2008-)
<i>Non TNF-α biologics:</i>	
Abatacept	L04AA24 (2008-)
Anakinra	L04AC03
Canakinumab	L04AC08 (2011-)
Ixekizumab	L04AC13
Rituximab	L01XC02 (2005-)
Sarilumab	L04AC14
Secukinumab	L04AC10
Tocilizumab	L04AC07 (2010-)
Ustekinumab	L04AC05 (2010-)
<i>Corticosteroids</i>	
Hydrocortison	H02BX
Prednisolon	H02AB
<i>Low-potency immunosuppressant</i>	
Apremilast	L04AA32
Chloroquin	P01AB01 (2005-)
Sulfasalazin	M01CX02 (2005-) A07EC01 (2005-)
<i>Intermediate-potency immunosuppressant</i>	
Baricitinib	L04AA37 (2018-)
Ciclosporin	L04AA01 (2005-2007) L04AD01 (2008-)
Hydroxychloroquin	P01BA02 (2005-)
Leflunomide	L04AA13 (2005-)
Mycophenolic acid	L04AA06
Tofacitinib	L04AA29 (2014-)
<i>High-potency immunosuppressant</i>	
Azathioprin	L04AX01 (2005-)
Methotrexate	L01BA01 L04AX03 M01CX01
Anti-dementia drug	
Donepezil	N06DA02
Anticholinesterases	N06DA03
Galantamine	N06DA04
Memantine	N06DX01

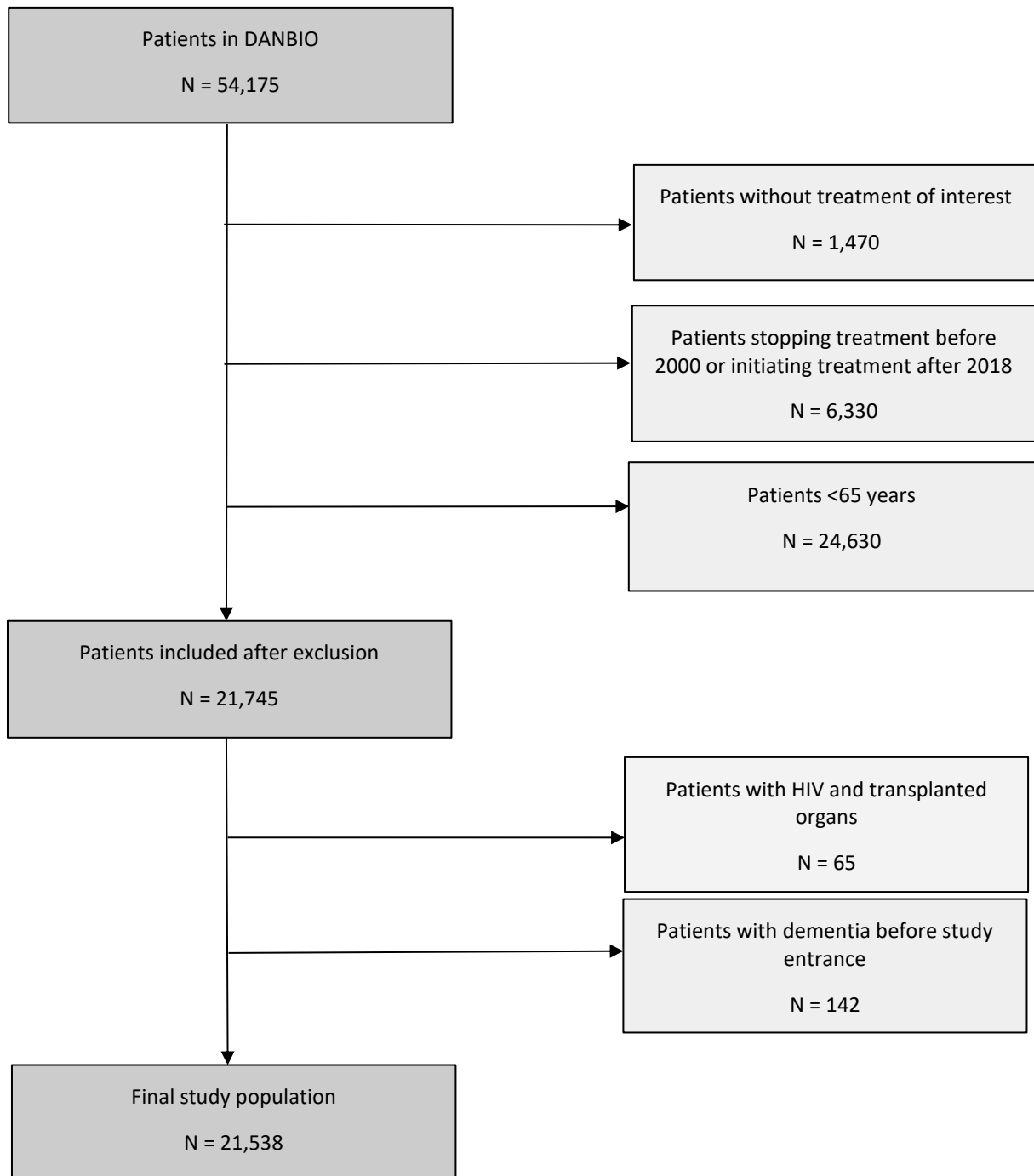
Diagnosis	ICD-8 codes / ICD-10 codes
Alzheimer's dementia	290.10 / F00.0-00.9, G30.0-30.9
Vascular dementia	293.09-19 / F01.0-01.9

Frontotemporal dementia	290.11 / F02.0
Dementia without specification	290.09, 290.19 / F03.9, G31.9
Other dementias	290.18 / G31.8

Supplement Table 2. Differences in available information in DANBIO and AOK PLUS

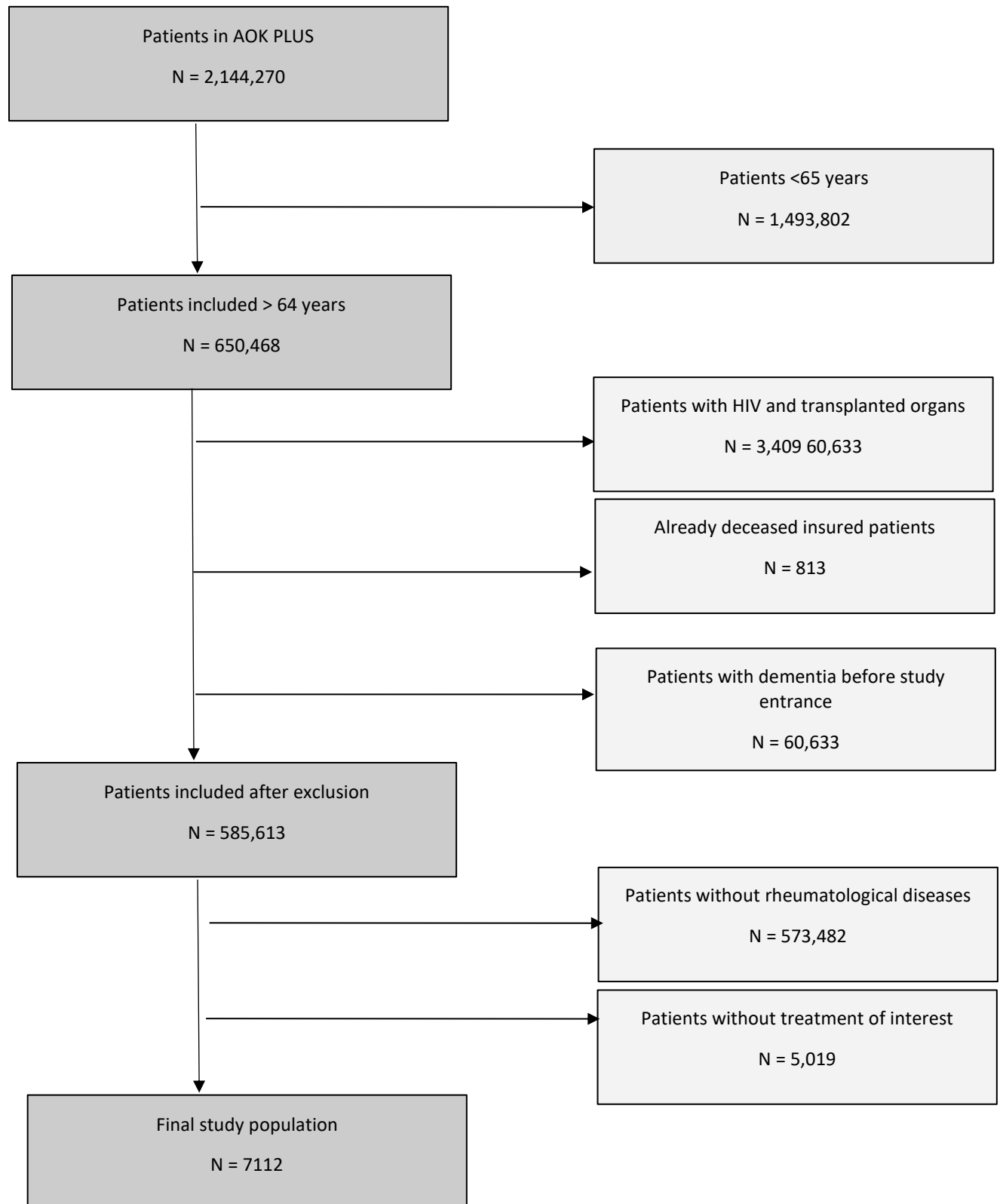
Indicator	DANBIO	AOK PLUS
<i>High-potency immunosuppressants</i>	Azathioprin Methotrexate	Azathioprin Methotrexate
<i>Intermediate-potency immunosuppressants</i>	Baricitinib Ciclosporine Hydroxychloroquin Leflunomide Mycophenolic acid Tofacitinib	Ciclosporin Leflunomide
<i>Low-potency immunosuppressants</i>	Apremilast Chloroquin Sulfasalazine	Chloroquine Hydroxychloroquine Sulfasalazine
<i>Non-TNF-Biologics</i>	Abatacept Anakinra Canakinumab Ixekizumab Rituximab Sarilumab Secukinumab Tocilizumab Ustekinumab	Abatacept Canakinumab Rituximab Tocilizumab Ustekinumab
<i>TNFi</i>	Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab
<i>Time</i>	Daily	Quarterly
<i>Time frame</i>	2000-2018	2005-2014
<i>Dementia</i>	Documented once with ICD-8 codes 290.09, 290.10, 290.11, 290.19, 290.18293.09-19 / ICD-10 codes F00/G30, F01, F02, F03, G31 and/or at least one prescription of an anti-dementia drug ATC codes: N06DA02, N06DA03, N06DA04, and N06DX01 in the Danish National Patient Register and the Danish National Prescription Registry	Documented once with ICD-10 codes F00/G30, F01, F02, F03 in outpatient care

Supplement Figure 1. Study flow diagram of inclusion and exclusion criteria in DANBIO



Supplement Figure 2. Study flow diagram of inclusion and exclusion criteria in AOK PLUS

PLUS



Supplement Table 3. Association with risk of dementia for each of the (non-TNFi) anti-inflammatory drug groups compared to nonusers of each group*

	HR (95% CI)	
	DANBIO	AOK PLUS
Non-TNF-biologics	0.76 (0.53; 1.09)	0.84 (0.62; 1.14)
Corticosteroids	0.96 (0.83; 1.12)	0.97 (0.77; 1.22)
Low-potency immunosuppressant	0.84 (0.72; 0.99)	0.91 (0.77; 1.08)
Intermediate-potency immunosuppressant	1.04 (0.77; 1.40)	0.88 (0.74; 1.05)
High-potency immunosuppressant	1.02 (0.82; 1.26)	0.91 (0.82; 1.01)

*Patients can be represented in more than one drug group, as they can use more than one anti-inflammatory drug.

Supplement Table 4. Association with incident dementia for each of the six drug groups compared to the 'mixed control group'*

	HR (95% CI)	
	DANBIO	AOK PLUS
TNFi	0.73 (0.62; 0.86)	0.68 (0.49; 0.95)
Non-TNF-biologics	0.60 (0.43; 0.86)	0.43 (0.33; 0.56)
Corticosteroids	0.77 (0.68; 0.87)	0.72 (0.71; 0.74)
Low-potency immunosuppressant	0.70 (0.61; 0.79)	0.78 (0.68; 0.89)
Intermediate-potency immunosuppressant	0.80 (0.60; 1.06)	0.75 (0.64; 0.88)
High-potency immunosuppressant	0.77 (0.72; 0.83)	0.76 (0.71; 0.82)

*The mixed reference group changes for each drug group comparison as it is represented by all individuals without use of the specific drug group exposure.