

SUOLISTON JA SUOLISTOMIKROBIEN MERKITYS PARKINSONIN TAUDISSA

Filip Scheperjans, neurologian erikoislääkäri, dosentti

HYKS Neurokeskus

Aava⁺

NeuroInnovation Oy

Helsingin yliopisto



SIDONNAISUUDET

Travel Support

AbbVie, Herantis, Global Kinetics, UCB, NordicInfu Care, Medtronic, Zambon

Grants

Academy of Finland, The Michael J. Fox Foundation for Parkinson's Research, The Finnish Medical Foundation, The Finnish Parkinson Foundation
Renishaw, Olvi Foundation, Stockmann Foundation, Aaltonen Foundation

Honoraria

AbbVie, Herantis, UCB, Zambon, LivaNova, Orion, GE Healthcare, Merck, Teva, Biogen, Bristol Myers Squibb, Sanofi

Other

Founder and CEO of NeuroInnovation Oy and Neurobiome Ltd., patents WO2015181449A1, US15314240, EP20150798909, FI20145492A

Scientific advisory board of Axial Biotherapeutics, MRM Health.



Parkinsonrannneke

MITATTUA TIETOA PARKINSONIN HOIDON TUEKSI

Mouth

- Pooling of saliva
- Problems with movements needed to brush teeth
- Jaw tremors

Oesophagus

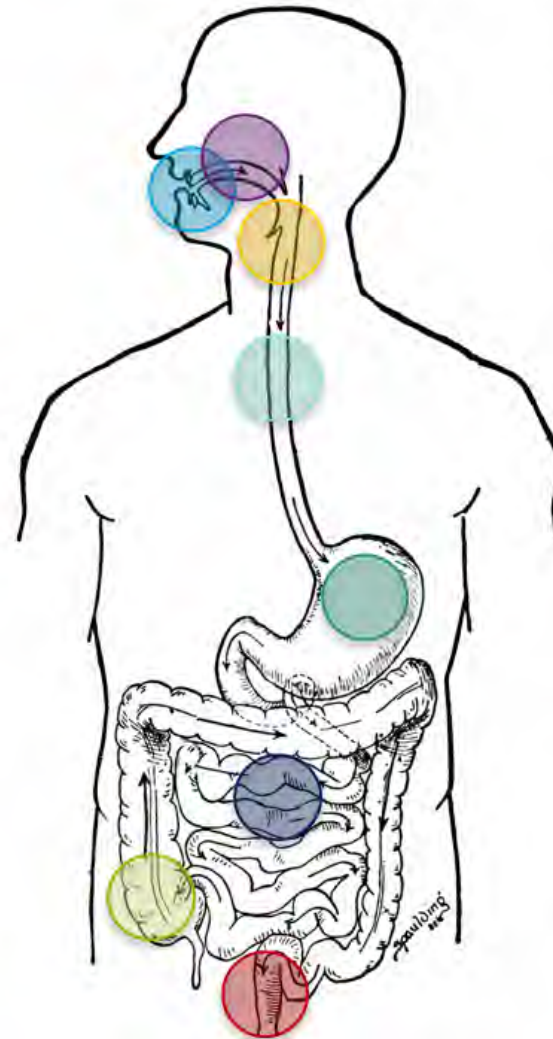
- Slow transit
- Segmental spasm
- Spontaneous contractions
- Air trapping
- Aperistalsis
- Gastro-oesophageal reflux

Small intestine

- Dilatation

Colon

- Colonic dysmotility
- Constipation
- Megacolon
- Volvulus
- Bowel perforation



Salivary Glands

- Reduced saliva production
- Low swallowing frequency causes drooling

Pharynx

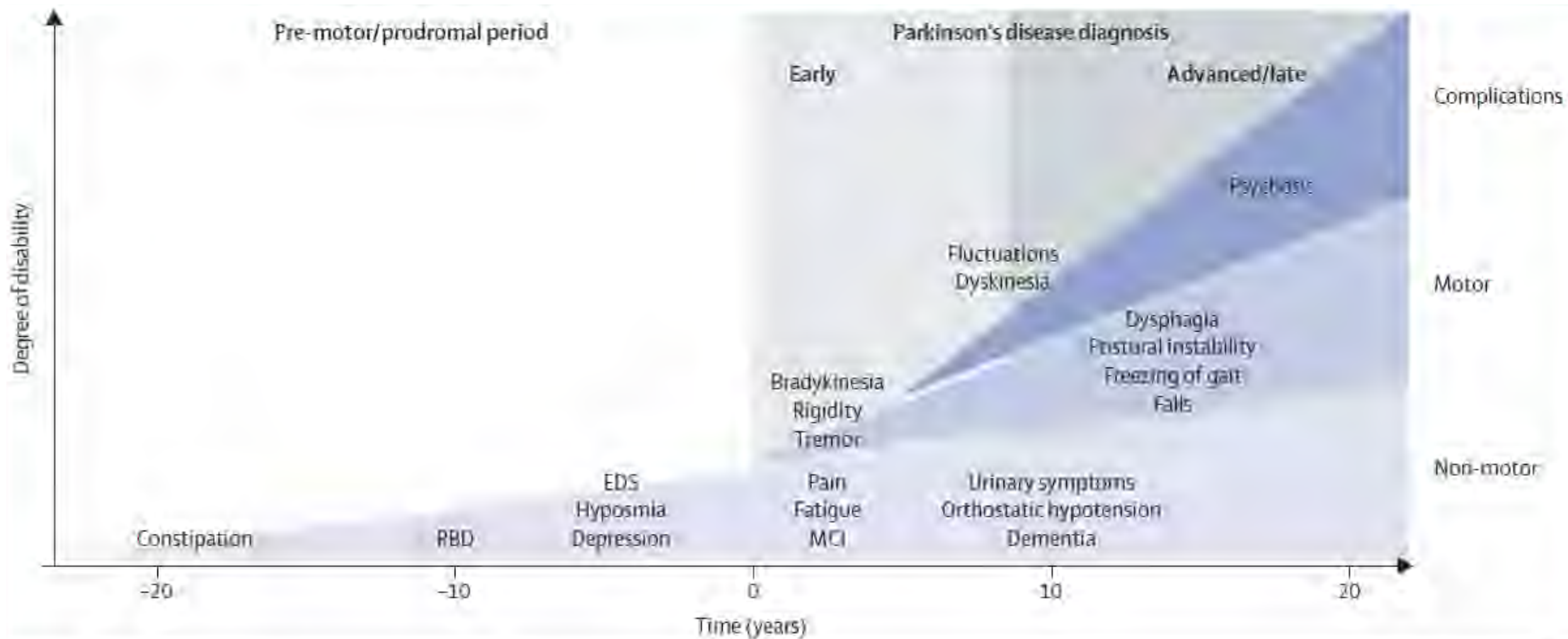
- Oropharyngeal dysphagia increases risk of aspiration

Stomach

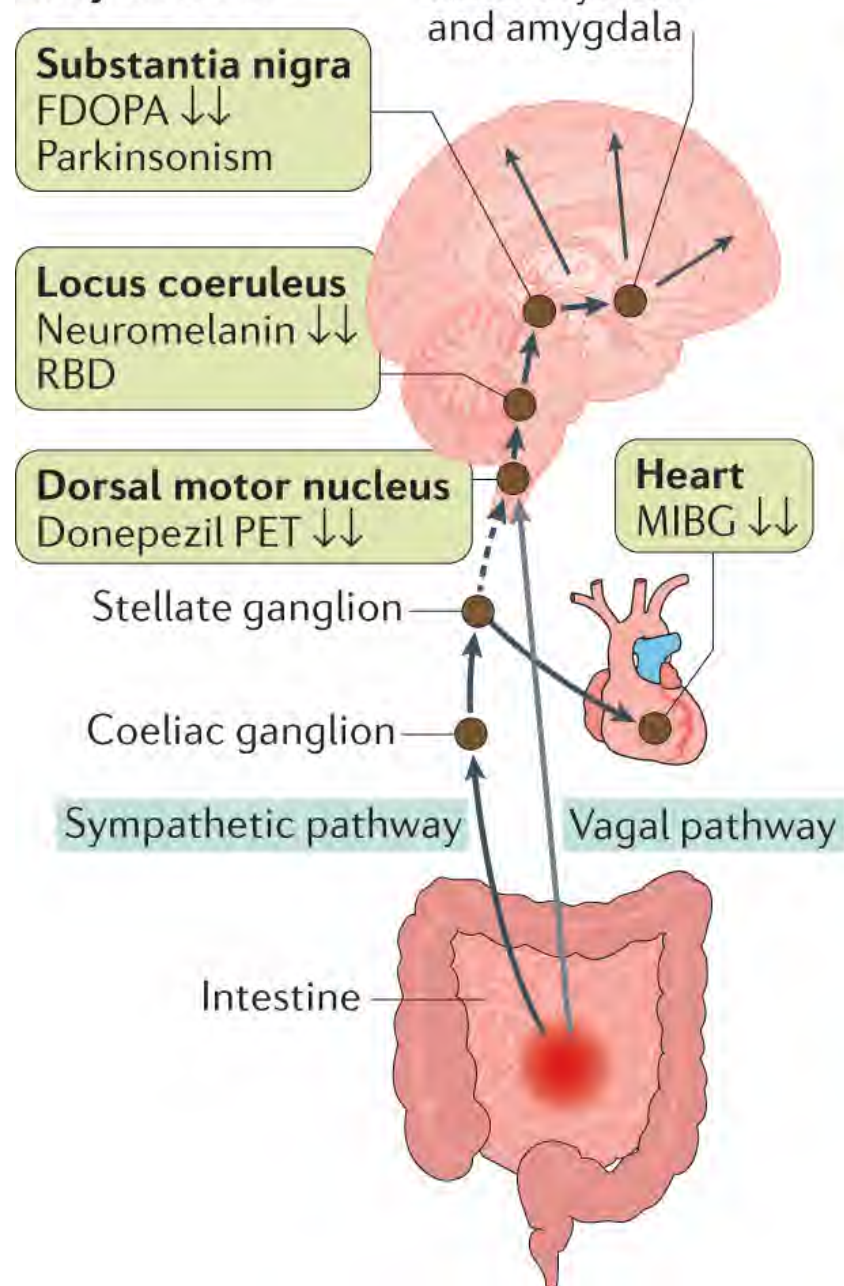
- Impaired gastric emptying:
 - Nausea
 - Bloating
 - Early satiety
 - Weight loss

Rectum

- Anorectal dysfunction leads to difficulty with defecation



Body-first PD



Brain-first PD

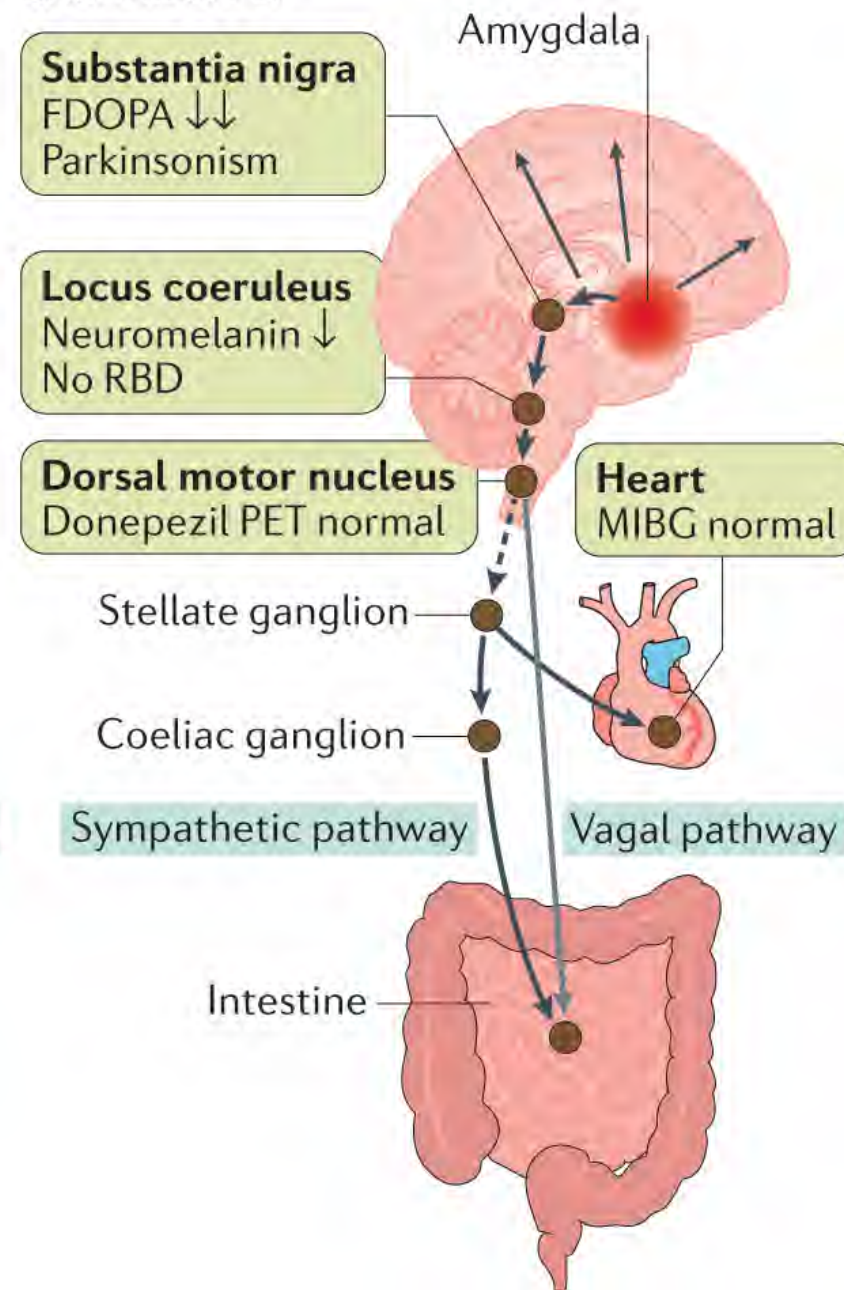


Table 2

Gastrointestinal adverse effects of commonly used motor medications in Parkinson disease

| Medications | Gastrointestinal Effects |
|---|--|
| Amantadine | Anorexia, constipation, diarrhea, dry mouth, dysphagia |
| Anticholinergics | Constipation, dry mouth, ileus, nausea, vomiting |
| Catechol O-methyltransferase inhibitors | Abdominal pain, anorexia, constipation, diarrhea, dry mouth, dyspepsia, flatulence, hepatic failure (tolcapone), nausea, vomiting |
| Dopamine agonists | Anorexia, abdominal cramps, constipation, diarrhea, dry mouth, dysphagia, epigastric pain, GI bleeding (bromocriptine), nausea, vomiting |
| Carbidopa/Levodopa | Abdominal pain, anorexia, constipation, diarrhea, dry mouth, dysphagia, nausea, vomiting, weight loss |
| Monoamine oxidase B inhibitors | Dry mouth, dyspepsia, nausea |

- Syyt
 - Syljeneritys on vähentynyt
 - nielemisen harventunutta ja tehotonta
 - etukumarrus
 - ilmeettömyys
- Esiintyvyys 10%-81%

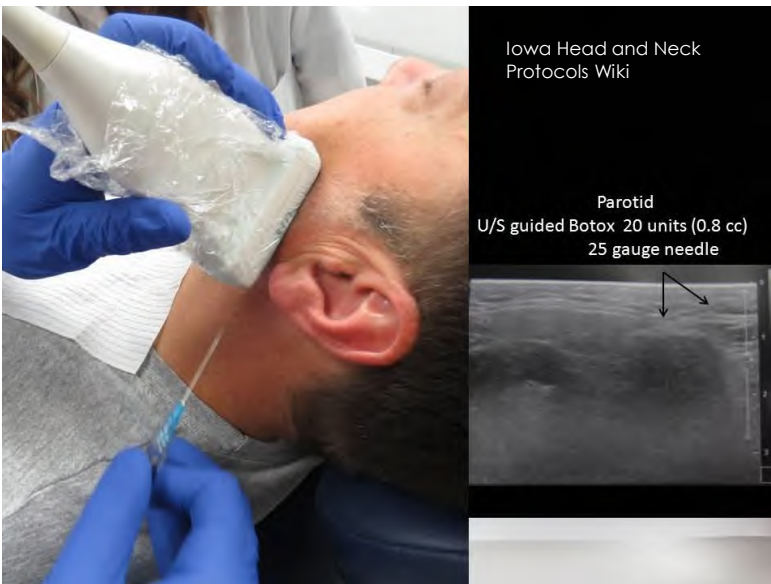


Bloem et al., Journal of Neurology 2009,256:1382–1383

| | | | |
|---------------------------|-----------------------|---|-------------------|
| Ipratropium Bromide Spray | Insufficient evidence | Insufficient evidence | Investigational |
| Glycopyrrolate | Efficacious | Insufficient evidence | Possibly useful |
| Botulinum Toxin B | Efficacious | Acceptable risk with specialized monitoring | Clinically useful |
| Botulinum Toxin A | Efficacious | Acceptable risk with specialized monitoring | Clinically useful |

Seppi et al. Mov Disord 2019

- Purukumi tai kovia karkkeja lisäävät nielemistä
- Lääkkeet paikallisesti tai suun kautta (sekavuus, ummetus)
- Suun kuivuminen voi johtaa hammasongelmiin

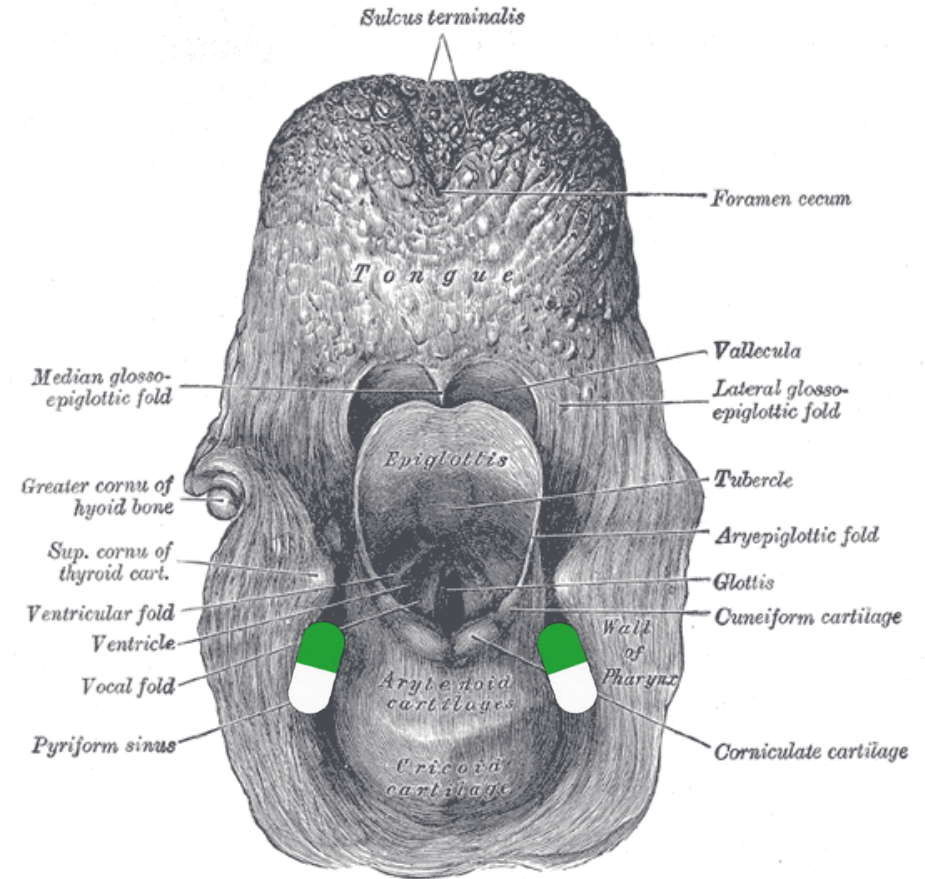


Pfeiffer RF. Parkinsonism Relat Disord 2011;17(1):10–5.

Hyson et al. Mov Disord 2002;17(6):1318–20

NIELEMISVAIKEUDET

- Esintyvyys ~35%, lisääntyy taudin edetessä
- Suun ja nielun ongelmat
 - pureskelu
 - tuntohäiriöt voivat heikentää yskimisrefleksin
 - tablettien jääminen limakalvotaskuihin altistaa tilanvaihteluille
- Ruokatorven häiriöt
 - mm. refluksi



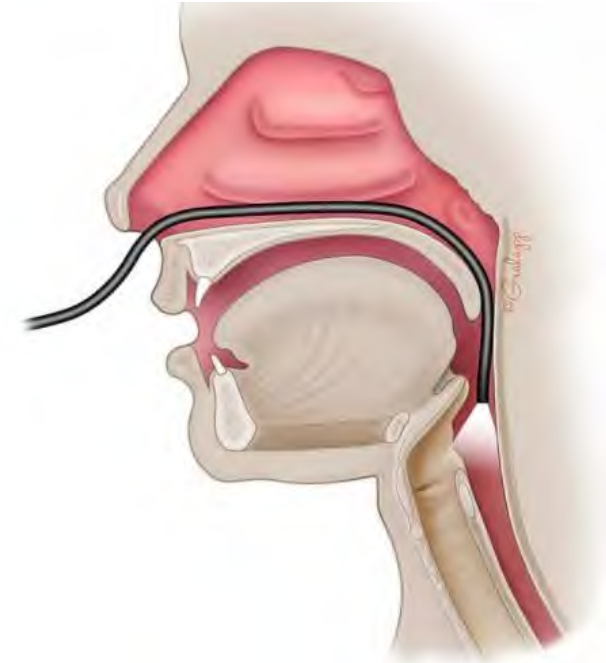
By Henry Vandyke Carter - Henry Gray (1918) Anatomy of the Human Body

NIELEMISVAIKEUDET

- Objektiiviset mittaukset
- Ruokavaliomuutoksia
- Puheterapeutin, fysioterapeutin ravitsemusterapeutin konsultaatio
- Levodopatablettien pureskelu tai liukenevat tabletit
- Laiteavusteiset hoidot



HUS^{*}

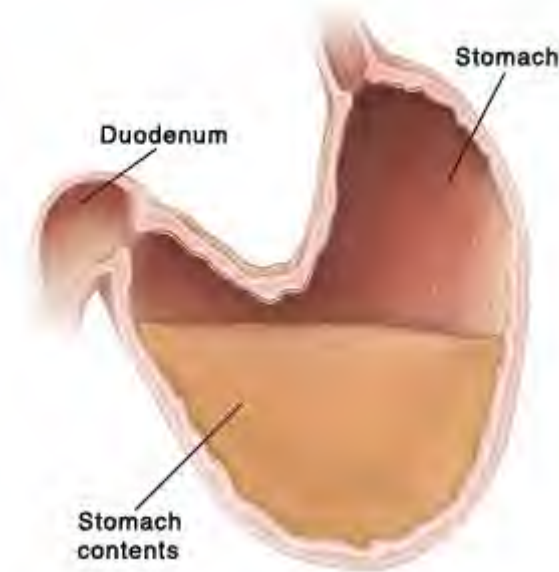


MAHALAUKUN HÄIRIÖT

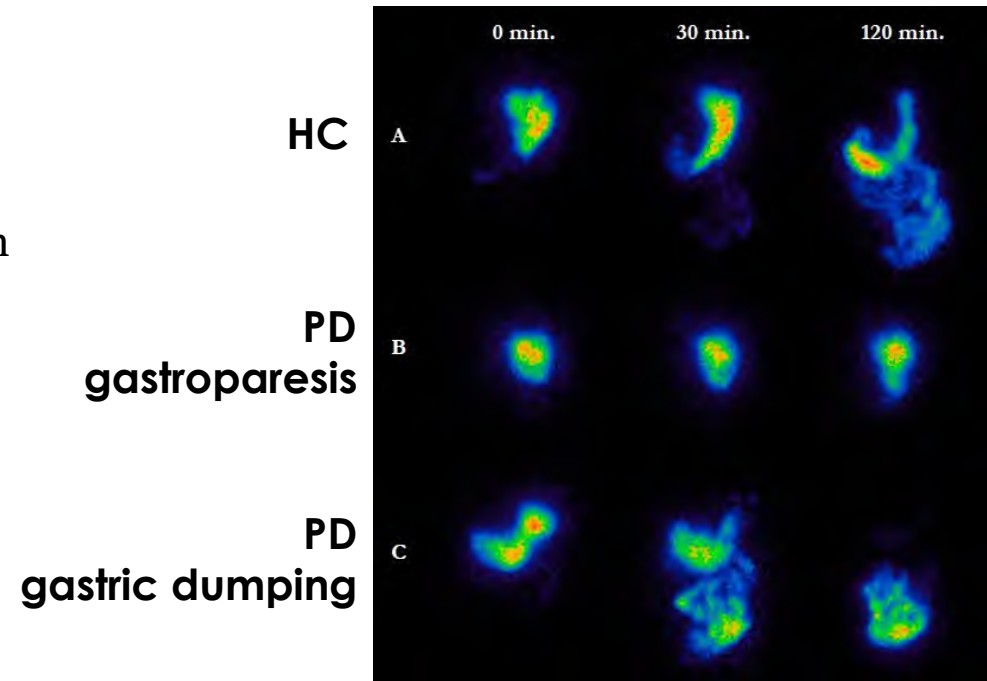
- Hidastunut tai nopeutunut tyhjeneminen
- Oireet
 - Voi olla oireeton
 - Ähky, pullotus, turvotus, ennenaikainen kylläisyys, ylävatsakipu
 - pahoinvointi, oksentelu

Hoito

- Ruokavaliomuutokset
 - monta pientä annosta, rasvan määrän vähentäminen
 - pystyasento ruokailun jälkeen 1-2 tuntia
- Lääkehoito

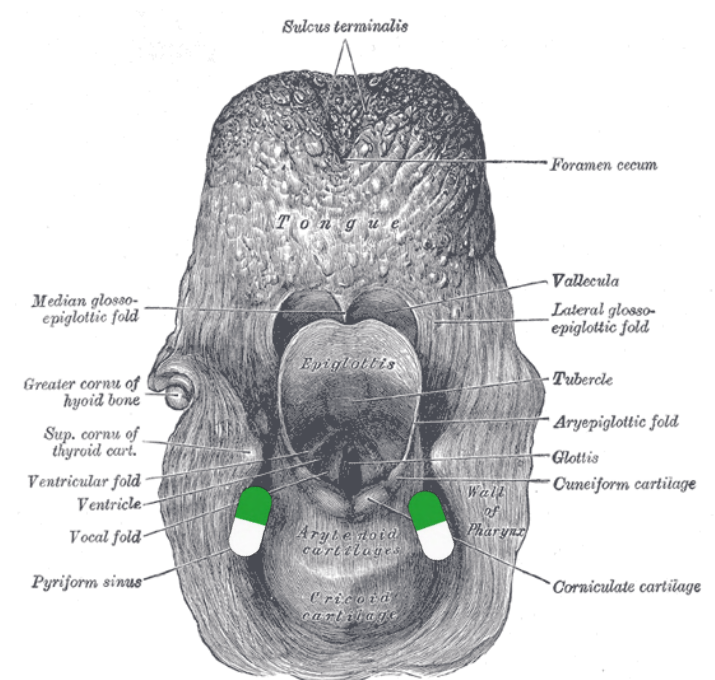
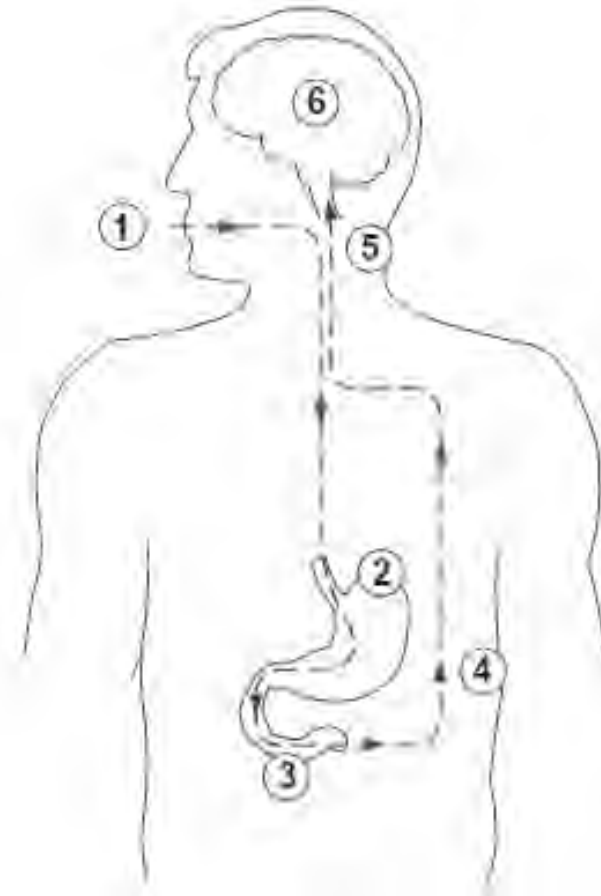


<http://www.uofmmedicalcenter.org/healthlibrary/Article/40462>



YLEMMÄN RUUANSULATUSKANAVAN HÄIRIÖIDEN MERKITYS TILANVAIHTELUISSA

- ① **Swallowing oral therapy**
Impaired swallowing (dysphagia) in advanced disease
- ② **Stomach**
Variable absorption of levodopa due to irregular gastric emptying
- ③ **Jejunum**
Competition with dietary amino acids for active transport across the intestinal wall
- ④ **Peripheral tissues**
Reduced levodopa bioavailability due to enzymatic breakdown by AADC and COMT
- ⑤ **Blood-brain barrier**
Competition for transport across the blood-brain barrier with large neutral amino acids limits the amount of levodopa reaching the striatum
- ⑥ **Striatum**
Conversion of levodopa to dopamine



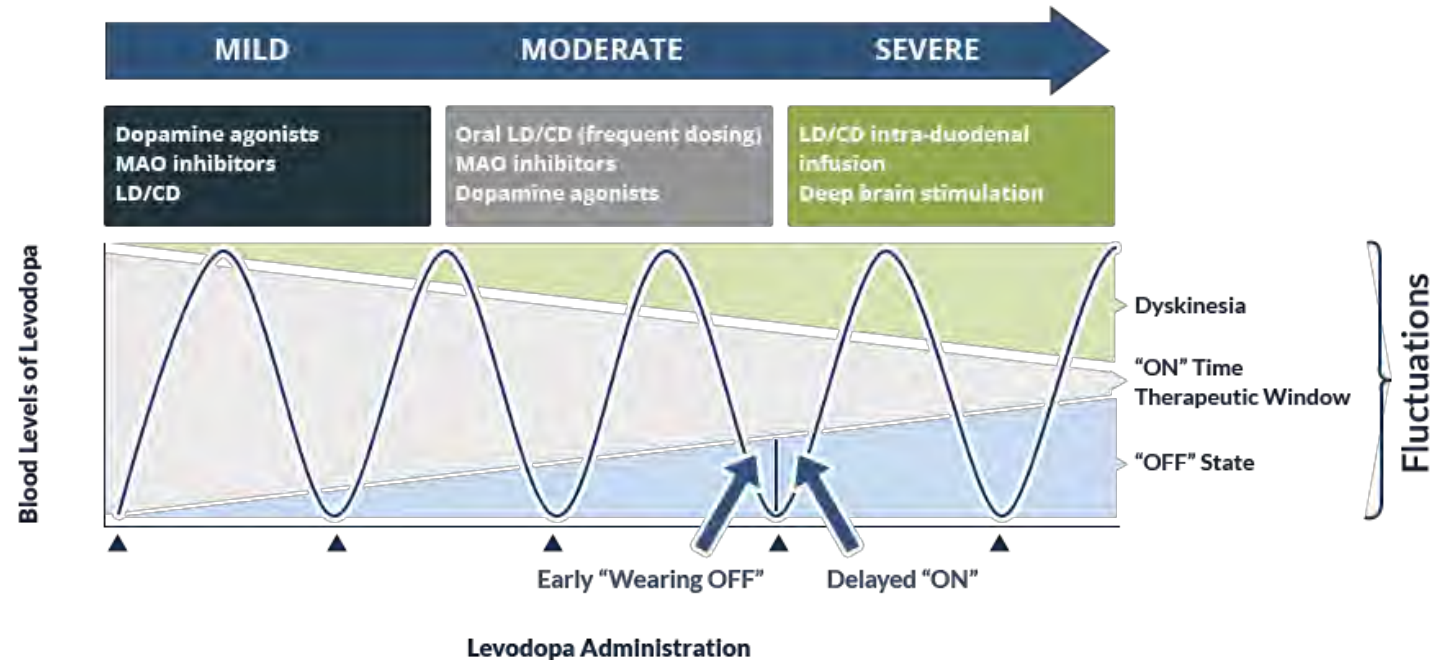
By Henry Vandyke Carter - Henry Gray (1918) Anatomy of the Human Body



Figure 2: Delay in gastric emptying
Photograph taken during gastroscopy. Arrow points to a carbidopa tablet remaining intact in a patient's stomach about 1.5 h after intake.

- Pakkoliikkeet **MUTTA MYÖS**

- Ahdistuneisuus
- Esteettömyys
- Levottomuus



- Hitaus
- Jäykkyys
- Vapina

MUTTA MYÖS

- Ahdistuneisuus
- Masennus
- Kipu
- Hengenahdistus
- Vatsaoireet
- Kävelypakko

YLEMMÄN RUUANSULATUSKANAVAN HÄIRIÖIDEN MERKITYS TILANVAIHTELUISSA

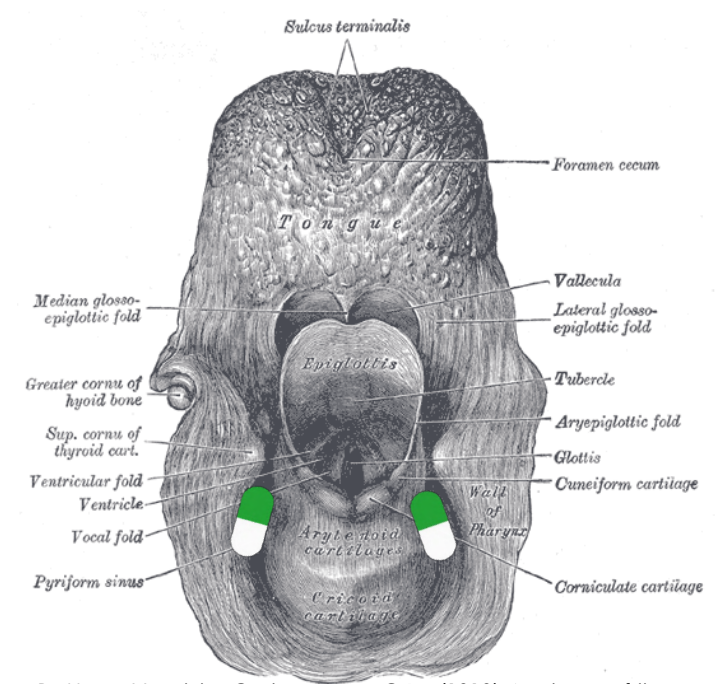
**Aivojen herkistyminen levodopan vaikutuksen
vaihtelulle**

+

Levodopan epäsäännöllinen imeytyminen

=

Epäsäännölliset tilanvaihtelut



By Henry Vandyke Carter - Henry Gray (1918) Anatomy of the Human Body



Figure 2: Delay in gastric emptying
Photograph taken during gastroscopy. Arrow points to a carbidopa tablet remaining intact in a patient's stomach about 1.5 h after intake.

Legge et al., Clin Geriatr Med 36 (2020) 81–92

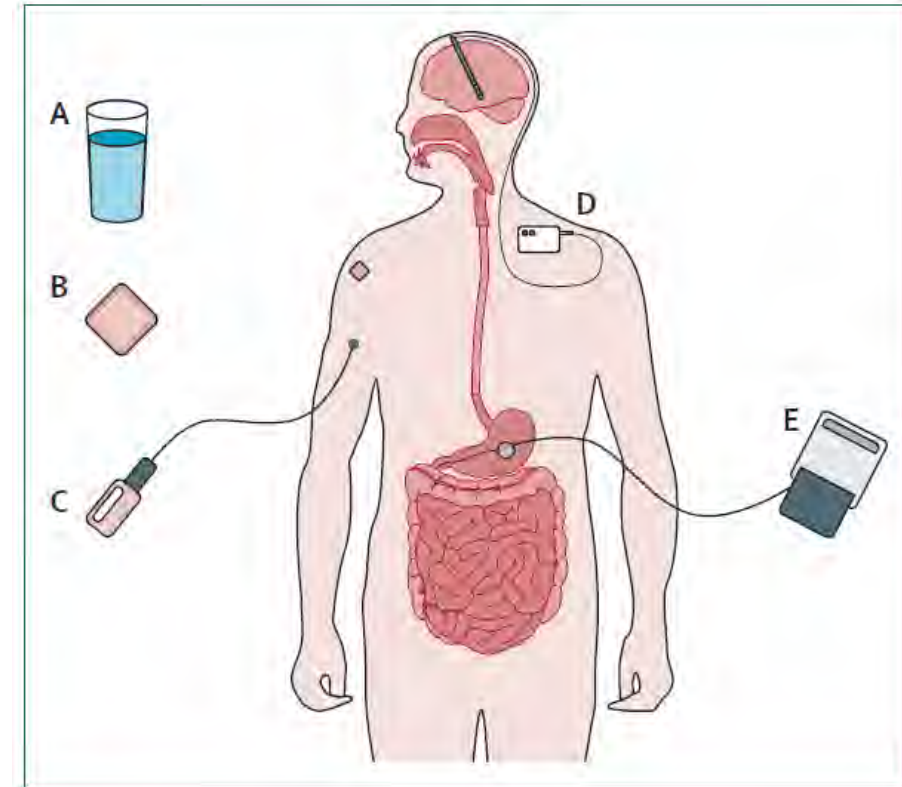
Skjærbæket al. J. Clin. Med. 2021, 10, 493

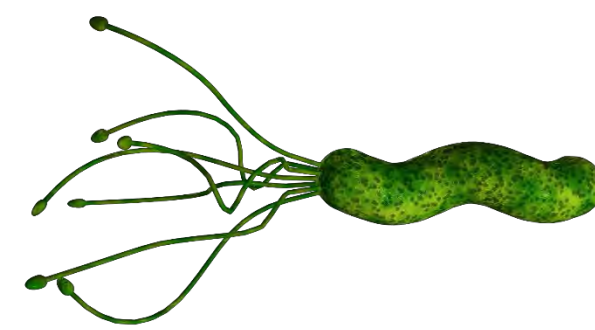
Fasano A et al. Lancet Neurol 2015;14(6):625–39.

Poewe et al. Clin Interv Aging . 2010 Sep 7;5:229-38

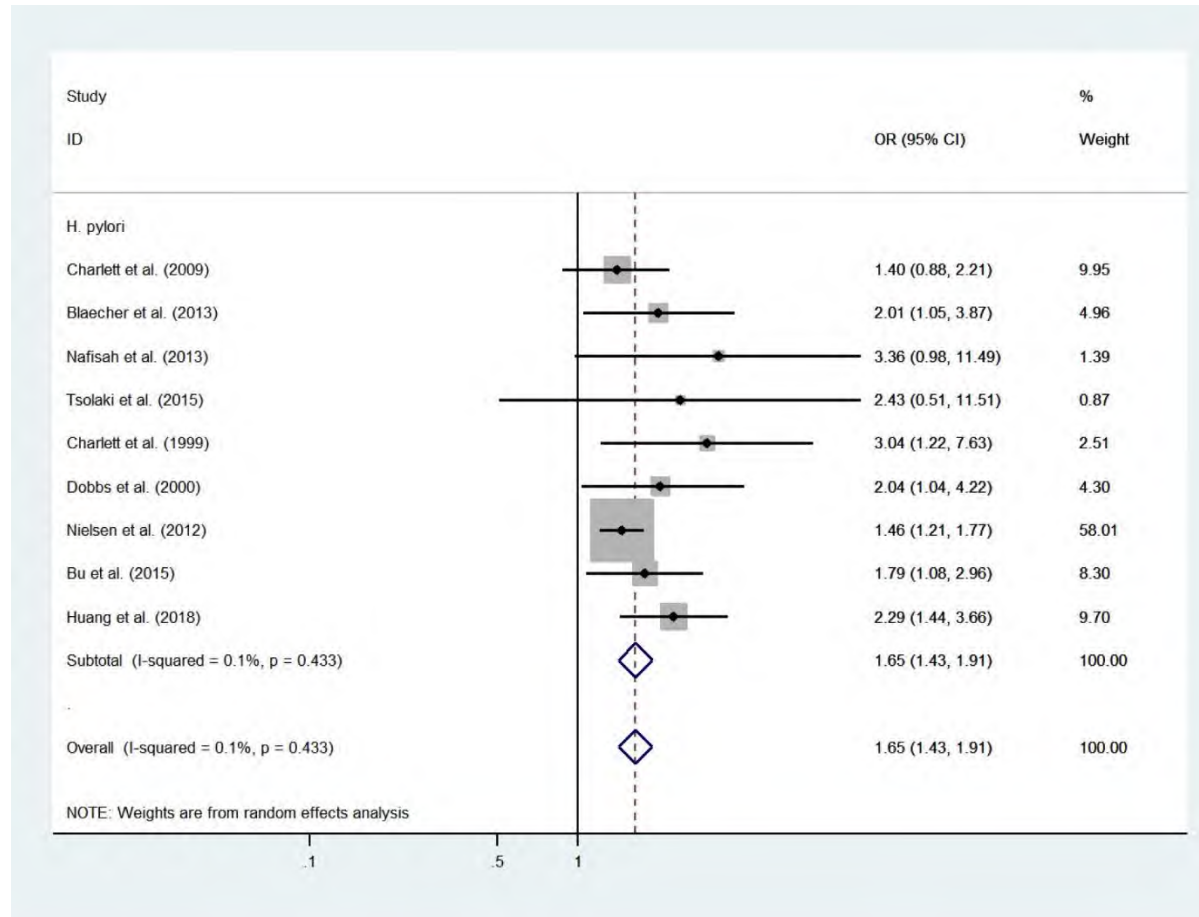
YLEMMÄN RUUANSULATUSKANAVAN HÄIRIÖIDEN MERKITYS TILANVAIHTELUISSA

- Nielemisvaikeudet ja ylemmän ruuansulatuskanavan häiriöt ovat tärkein syy hallitsemattomille tilanvaihteluille edenneessä Parkinsonin taudissa.
- Riittävä ajallinen ero lääkkeenoton ja ruokailun välillä on tärkeä mutta ei aina riittävä.
- Tablettien pureskelu tai liukeneva muoto voi helpottaa lääkkeen imeytymistä.
- Tässä tilanteessa oireiden optimaalinen hoito on haastava ja tulisi harkita laiteavusteisia hoitomuotoja.





H. pylori ja Parkinson



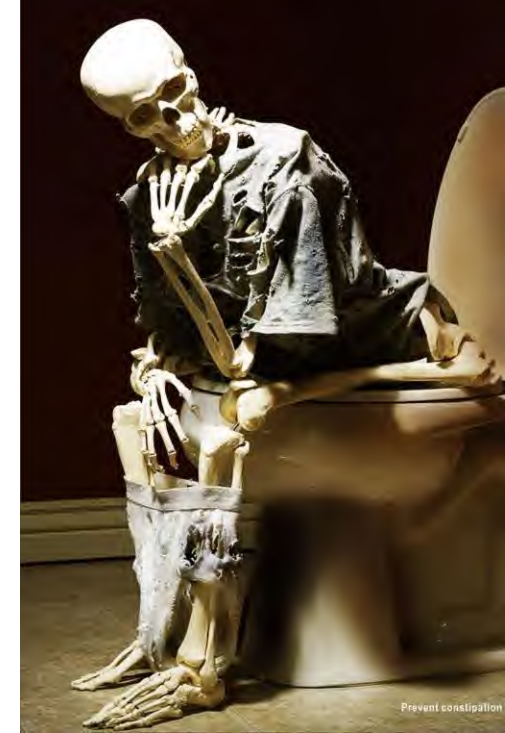
Helikobakteeria kannattaa etsiä ja tarvittaessa häätää, erityisesti potilailla, joilla on ylävatsaoireita ja hankalia tilanvaihteluita.








UMMETUS

- ~50% Parkinson-potilaista kärsivät ummetuksesta mutta suolen hidastunutta toimintaa voidaan todeta jopa 80%:lla.
- Monesti ummetus edeltää Parkinsonin liikehäiriöoireita.

- **HITAAN LÄPIKULUN UMMETUS**

- Kovat ulosteet



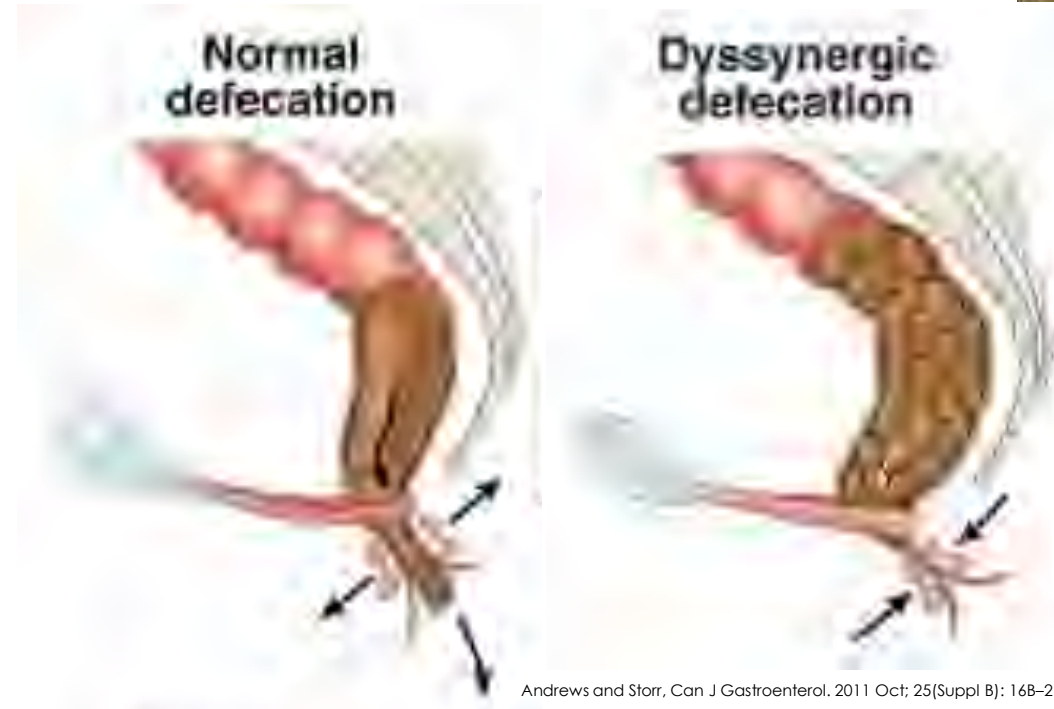
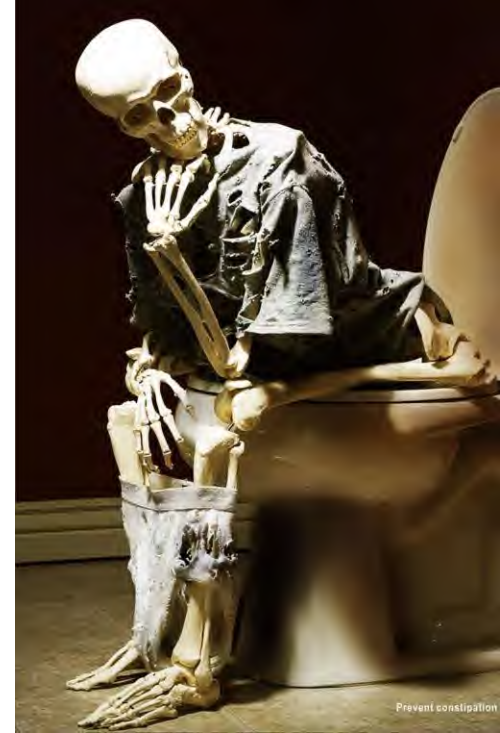
| BRISTOL STOOL CHART | | | |
|---|--------|--|----------------------------|
|  | Type 1 | Separate hard lumps | SEVERE CONSTIPATION |
|  | Type 2 | Lumpy and sausage like | MILD CONSTIPATION |
|  | Type 3 | A sausage shape with cracks in the surface | NORMAL |
|  | Type 4 | Like a smooth, soft sausage or snake | NORMAL |
|  | Type 5 | Soft blobs with clear-cut edges | LACKING FIBRE |
|  | Type 6 | Mushy consistency with ragged edges | MILD DIARRHEA |
|  | Type 7 | Liquid consistency with no solid pieces | SEVERE DIARRHEA |

UMMETUS

- ~50% Parkinson-potilaista kärsivät ummetuksesta mutta suolen hidastunutta toimintaa voidaan todeta jopa 80%:lla.
- Monesti ummetus edeltää Parkinsonin liikehäiriöoireita.

- **ULOSTAMISHÄIRIÖ**

- liikehäiriöoire
- ponnistelun tarve
- kipu
- epätäydellinen tyhjennys
- esteen tunne

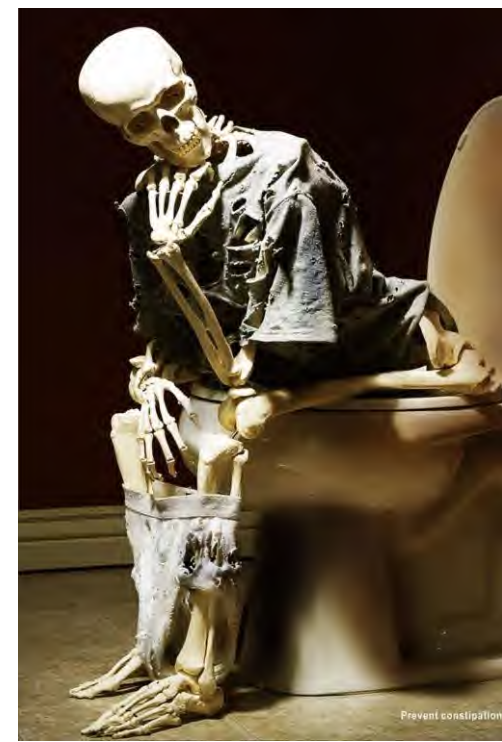


UMMETUS

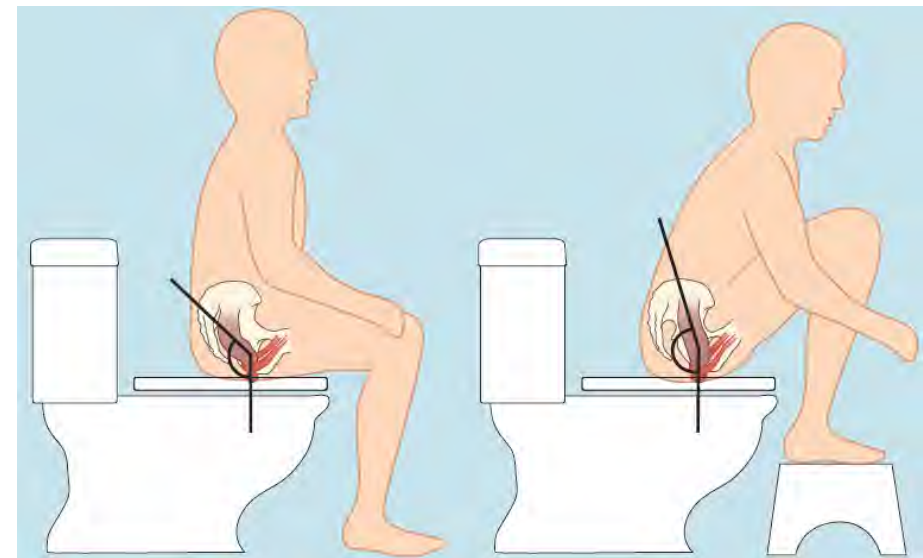
- HITAAAN LÄPIKULUN UMMETUS



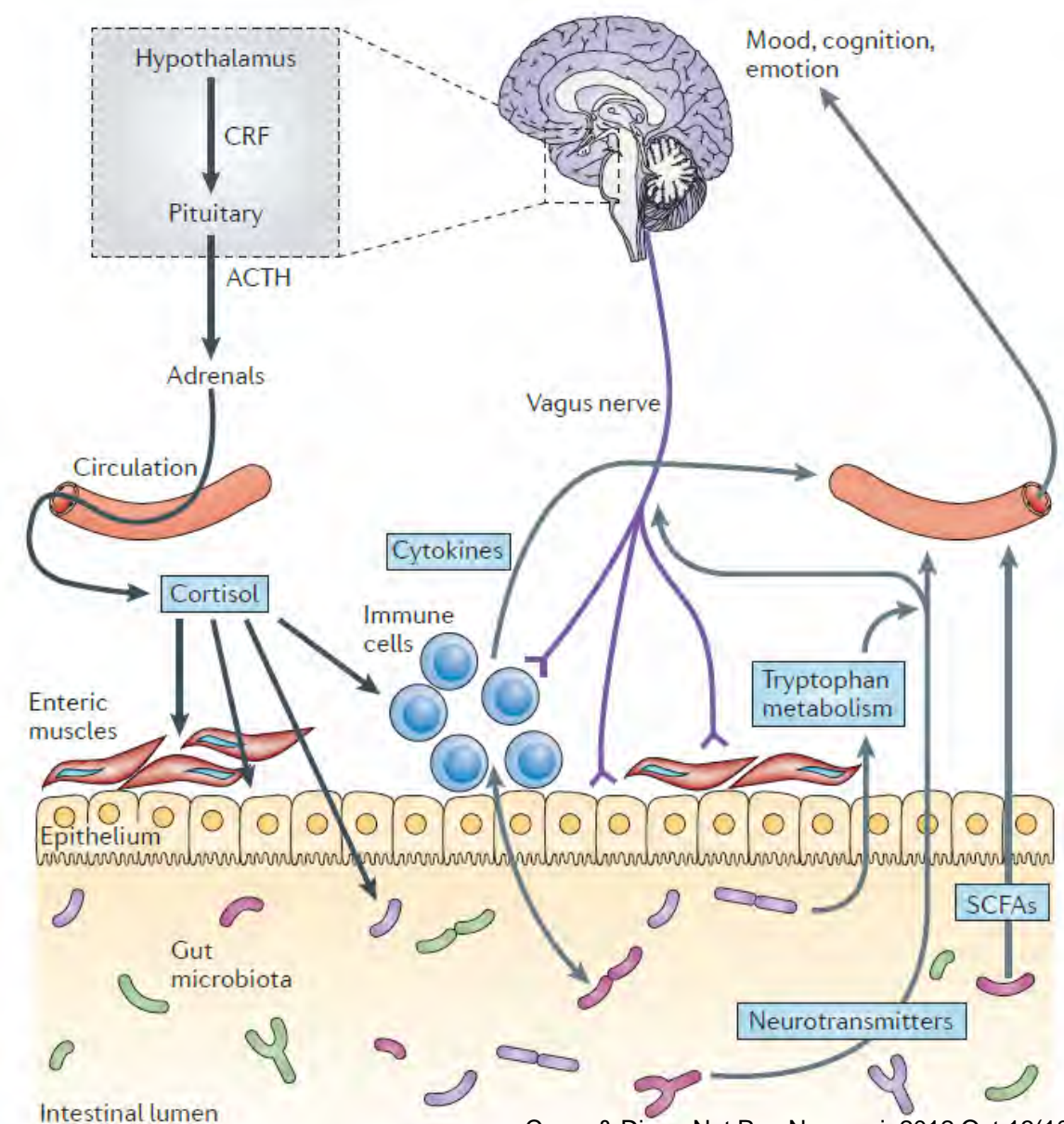
30-60g / päivä

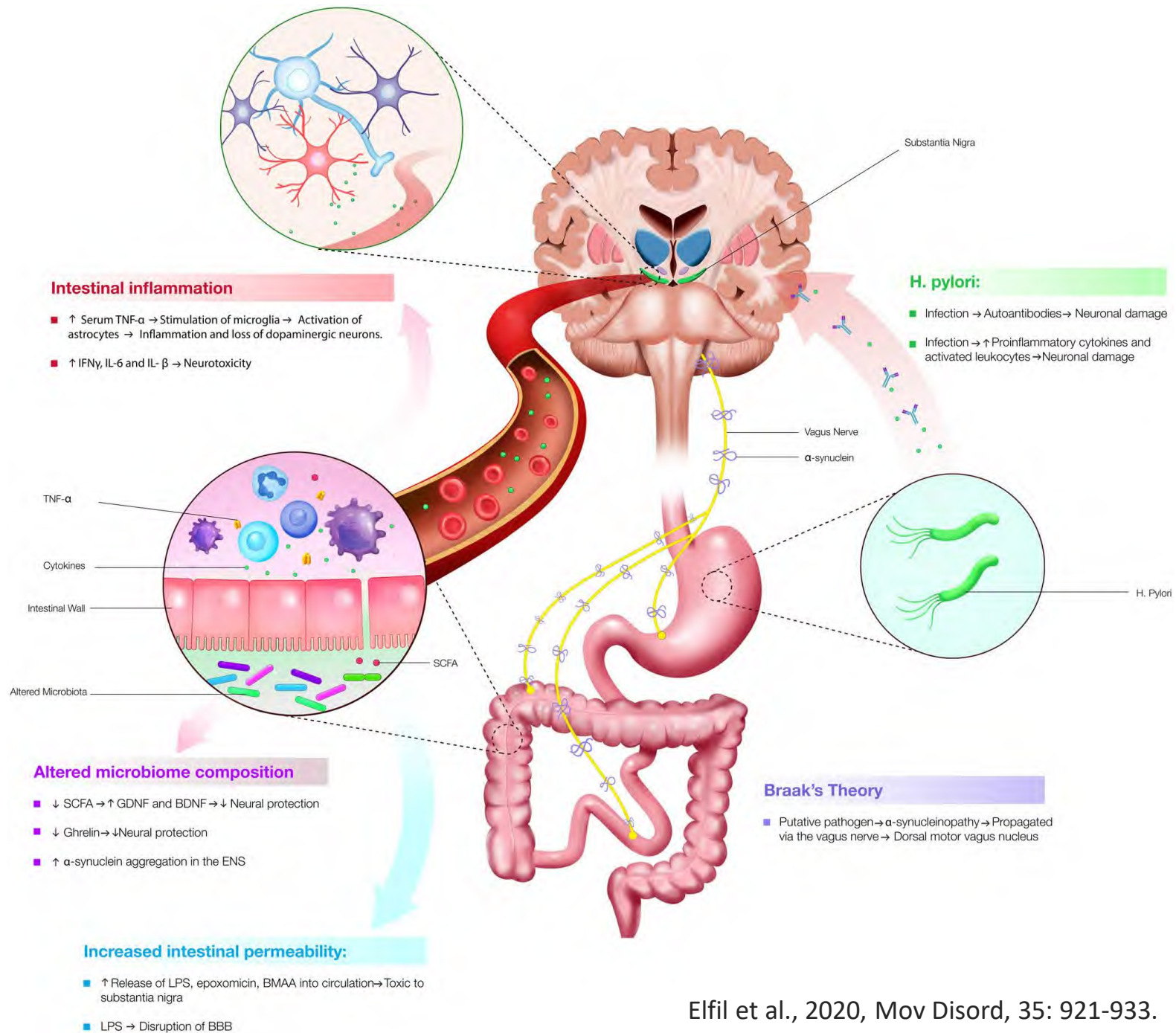


- HITAAN LÄPIKULUN UMMETUS
 - Mahdollisesti pahentavat lääkkeet?
 - MAKROGOLI (annosmuutokset hitaasti)
 - Stimuloiva ummetuslääke tarvittaessa muutaman päivän välein
 - Probiootit
 - Muut lääkkeet
- ULOSTAMISHÄIRIÖ
 - Motorinen oire, johon Parkinson-lääkitys voi auttaa
 - Ulosteen koostumus voi olla normaali
 - Peräruiskeet, perähuuhtelut
 - Botuliinihoito



- Mikrobisto/Mikrobiota
- Bakteerit, arkeat, protistit, sienet, virukset
- Ihmisen kehossa elää 10-100 biljoonaa bakteeria (1-10 kertainen määrä ihmissolujen määrään nähden).
- Valtaosa elää paksusuolella.
- Näissä mikrobeissa oleva geenimäärä on n. 100-kertainen ihmisgenomiin verrattuna.

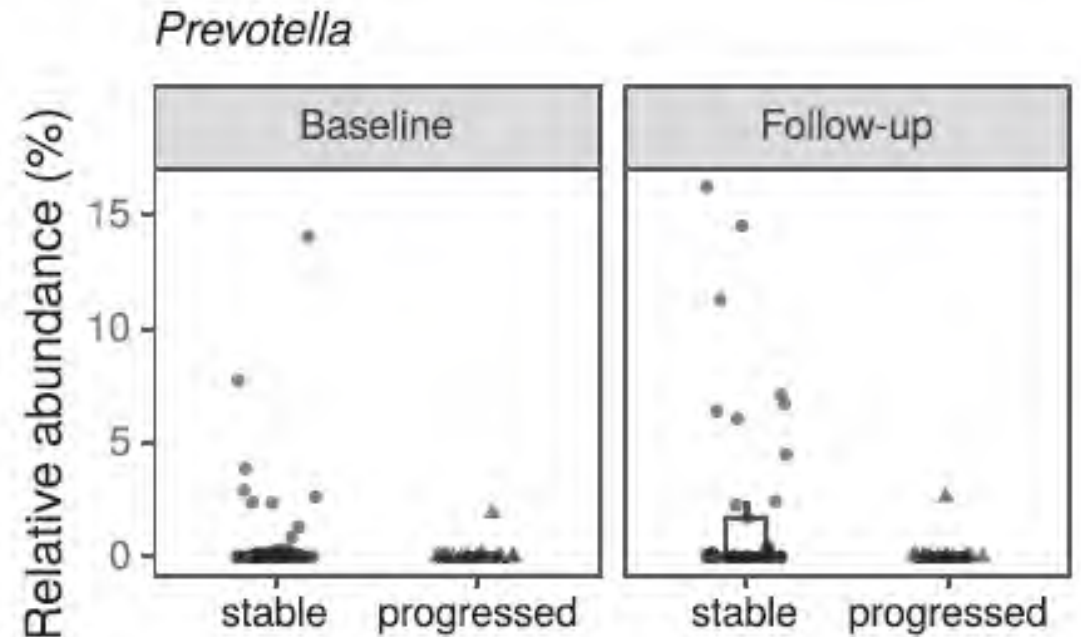
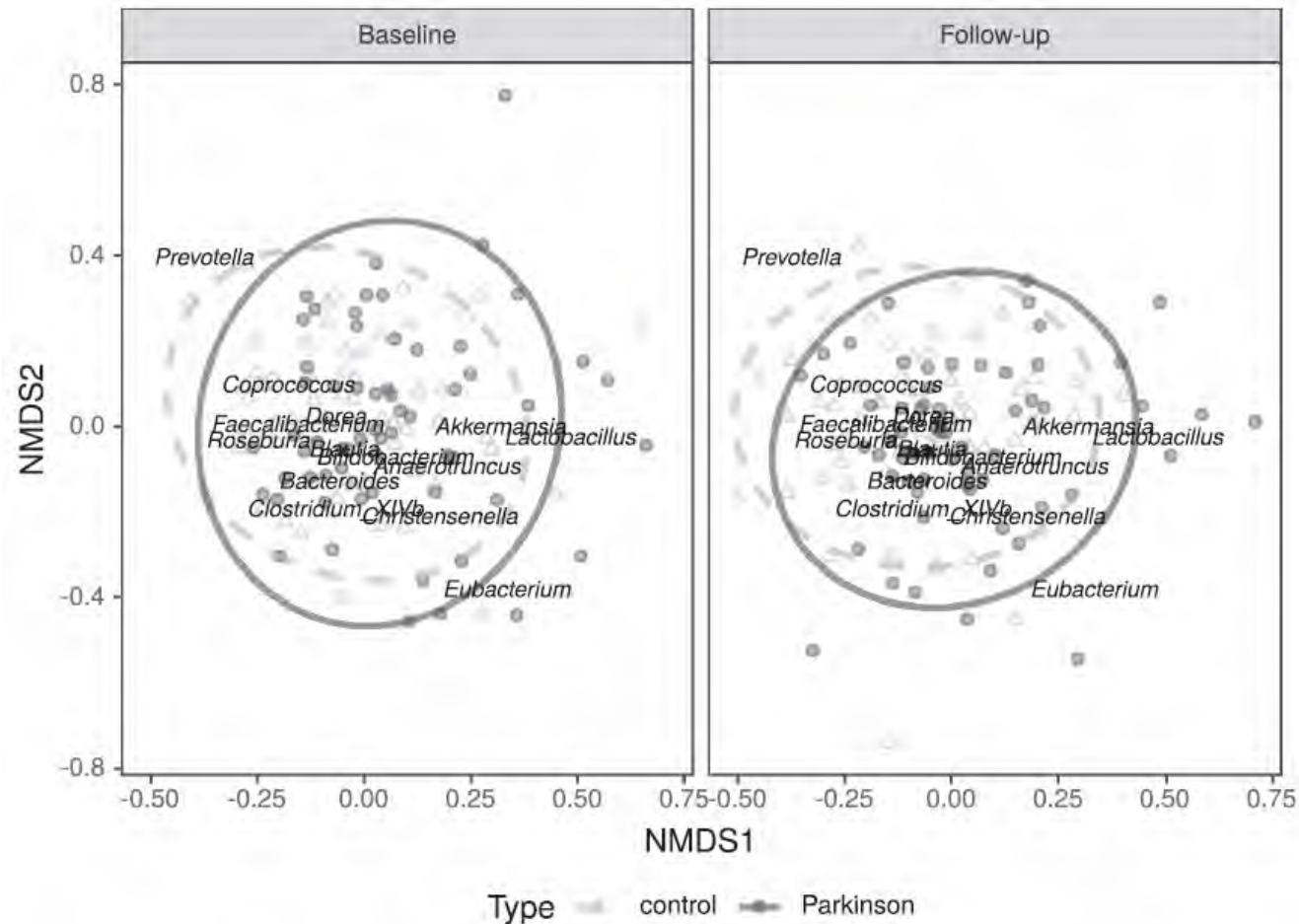





Research paper

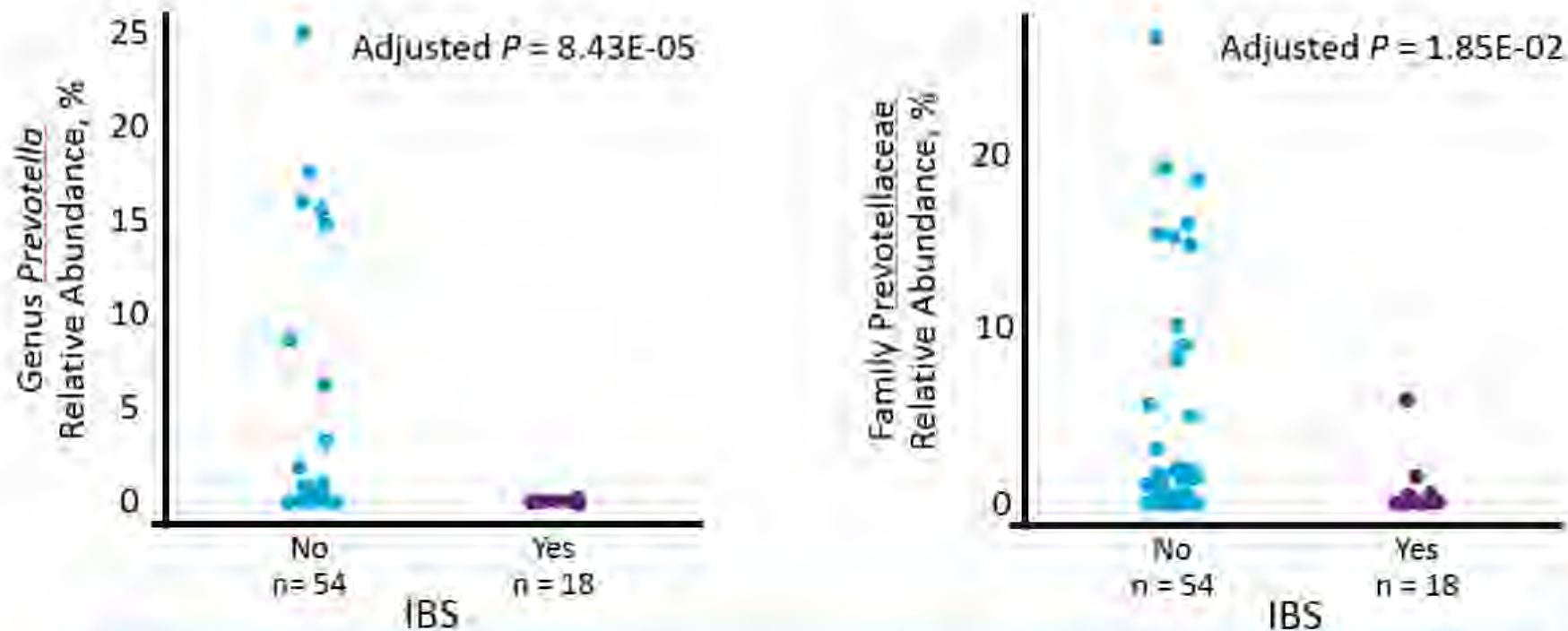
Gut microbiota in Parkinson's disease: Temporal stability and relations to disease progression

Velma T.E. Aho ^{a,b}, Pedro A.B. Pereira ^{a,b}, Sari Voutilainen ^c, Lars Paulin ^a, Eero Pekkonen ^b, Petri Auvinen ^a, Filip Scheperjans ^{b,*}



More than constipation – bowel symptoms in Parkinson's disease and their connection to gut microbiota

T. H. Mertsalmi^{a,b}, V. T. E. Aho^c, P. A. B. Pereira^c, L. Paulin^c, E. Pekkonen^{a,b}, P. Auvinen^c and F. Scheperjans^{a,b} 



- Symptoms that are IBS-like are *more prevalent* in patients with PD than controls
- Patients with IBD-like symptoms had *lower fecal abundance* of *Prevotella* bacteria

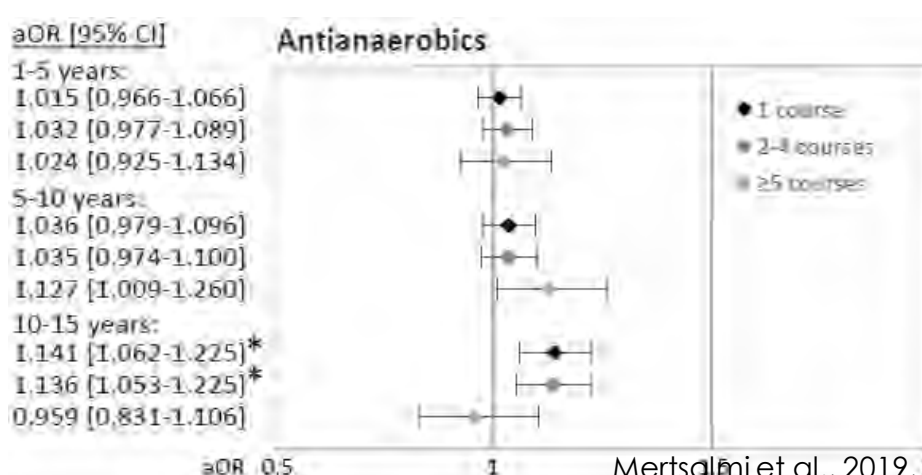
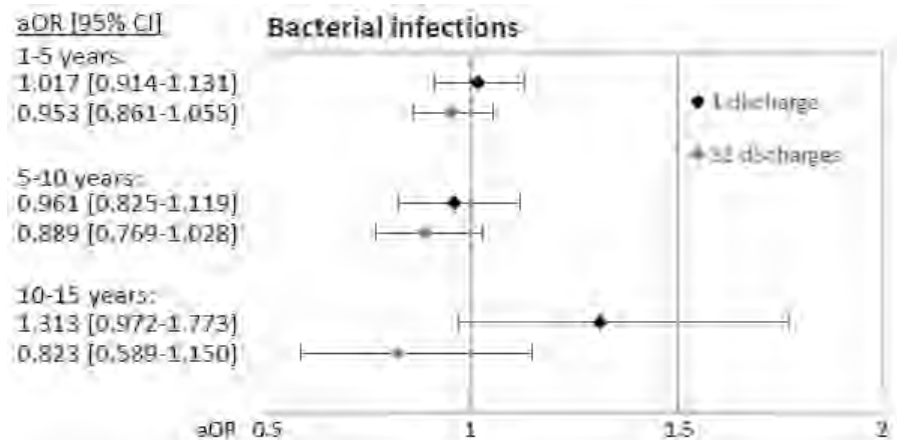
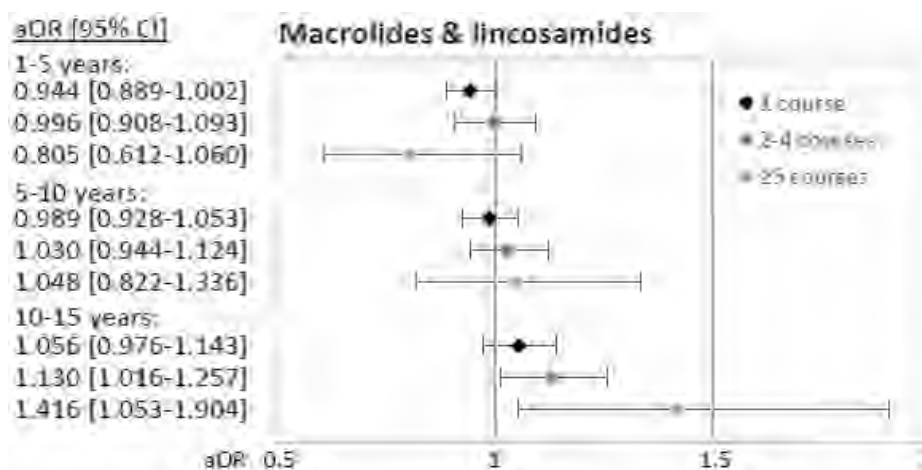
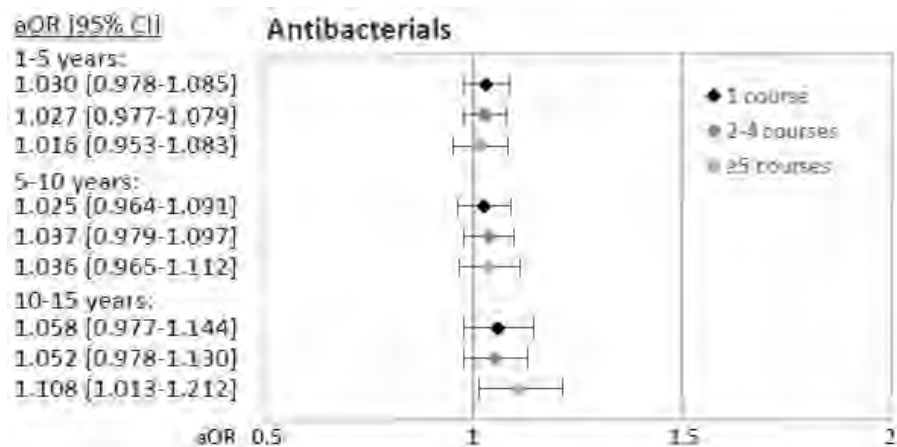
ANTIBIOTTIEN KÄYTTÖ JA PARKINSONIN TAUDIN RISKI

13976 Parkinson's disease patients

40697 matched controls

Follow-up on average 14.4 years

Adjusted for: IBD, IBS, COPD, TIA/stroke, CCI, *H. pylori* eradication, viral infections



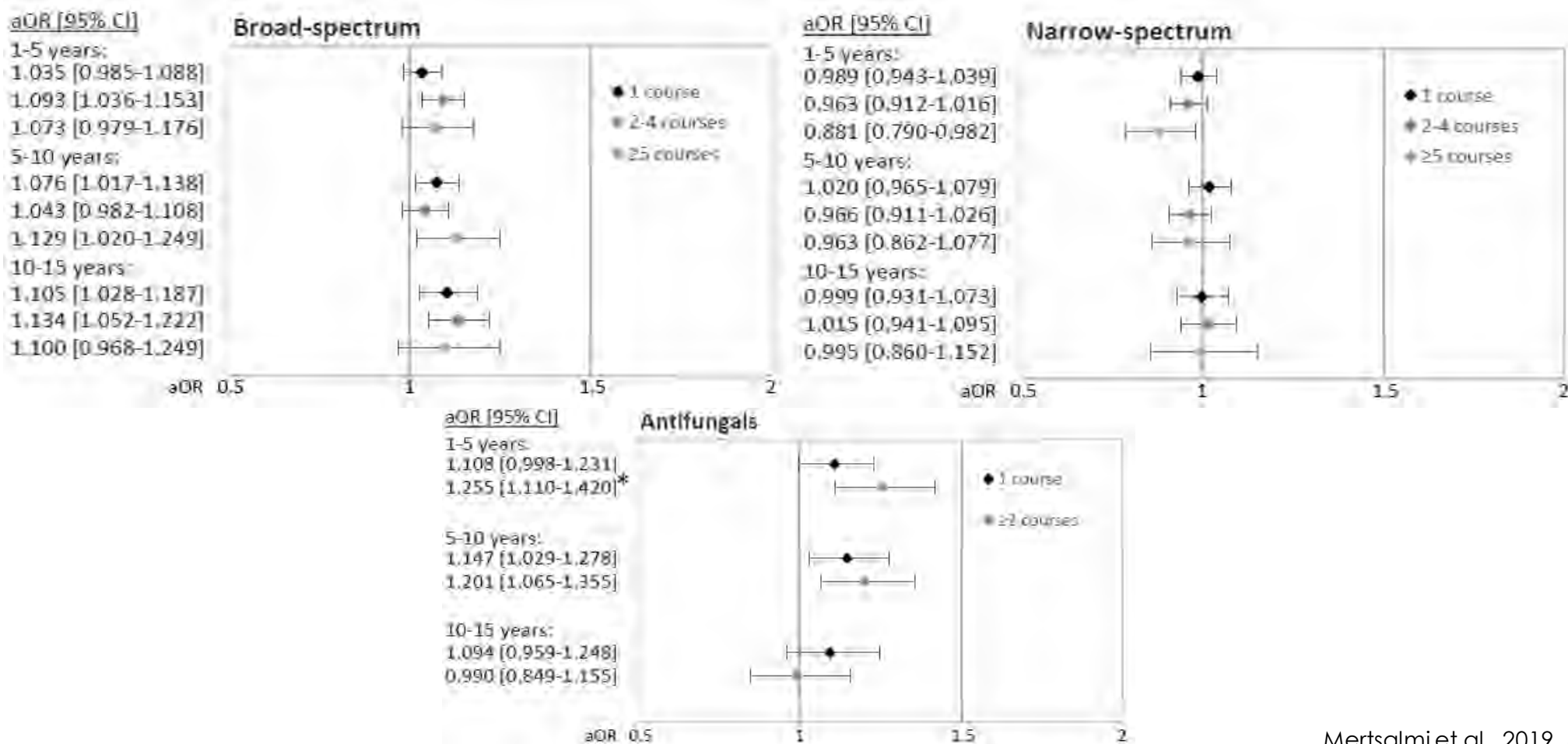
ANTIBIOTTIEN KÄYTTÖ JA PARKINSONIN TAUDIN RISKI

13976 Parkinson's disease patients

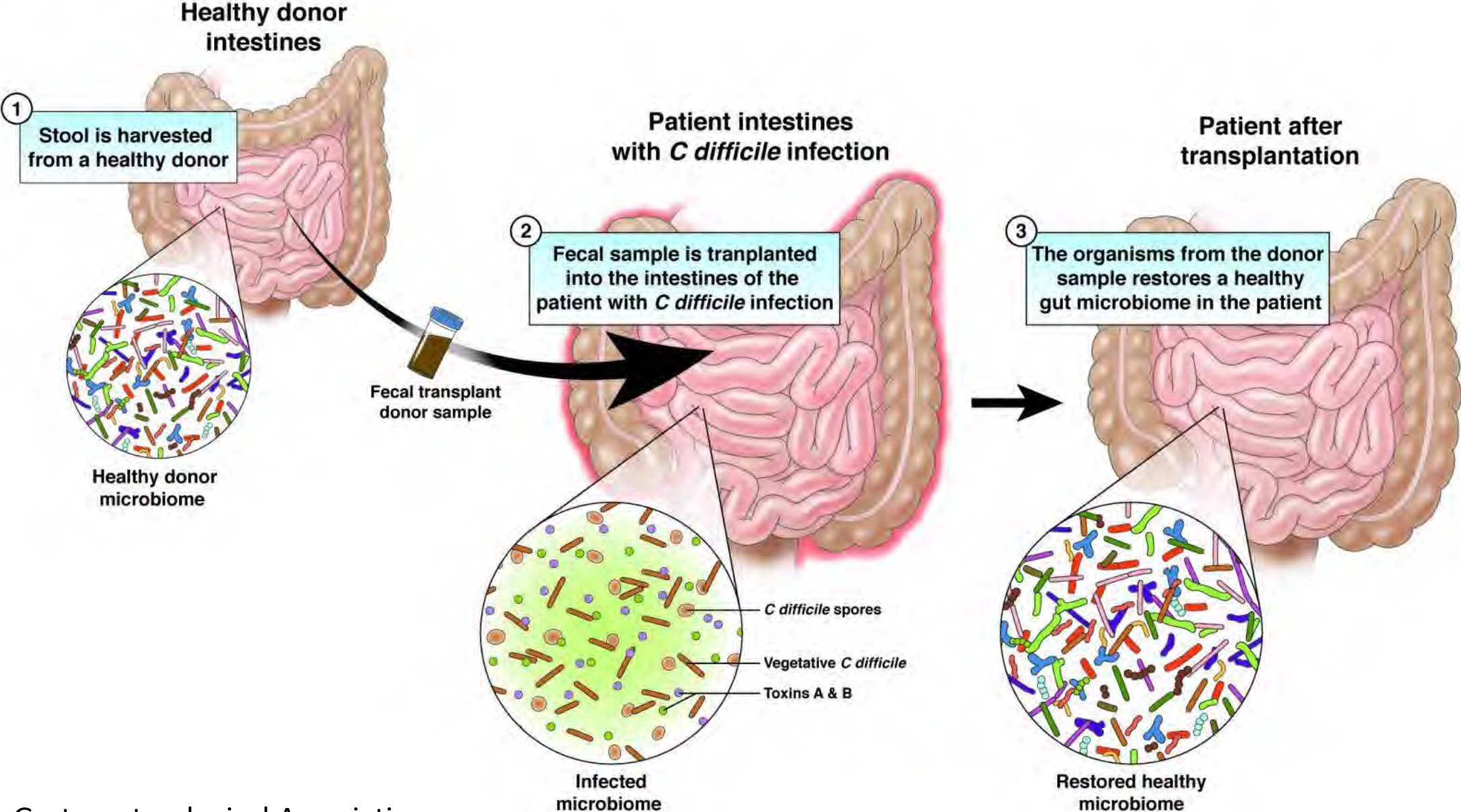
40697 matched controls

Follow-up on average 14.4 years

Adjusted for: IBD, IBS, COPD, TIA/stroke, CCI, *H. pylori* eradication, viral infections



ULOSTEENSIIRTO



ULOSTEENSIIRTO PARKINSONIN TAUDISSA

Xue et al., 2020, Medicine

Kontrolloimaton

10 paksusuolen tähyystyksellä

5 nenämahaletkulla

Kuai et al., 2021, Microb Cell Fact

ummetuspotilaat, kontrolloimaton

11 nenämahaletkulla

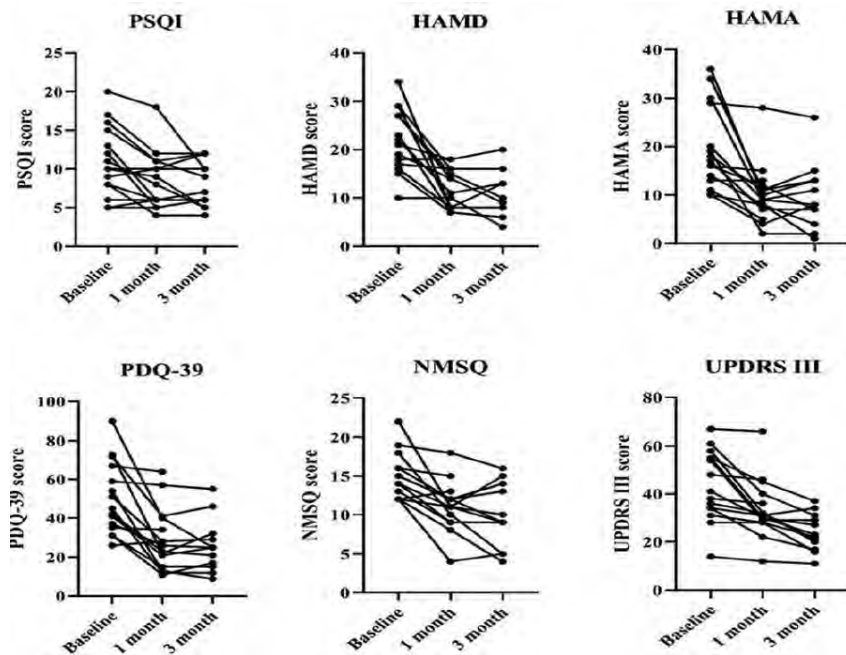


Table 2 Outcome measures in the participants

| | Before FMTa | 6 weeks After FMT | 12 weeks After FMT | p-value |
|----------------------------|----------------|-------------------|--------------------|---------|
| BMI (mm/kg ²) | 22.01 ± 1.73 | 23.52 ± 1.65 | 24.65 ± 1.09 | |
| H-Y Grade** | 2.27 ± 0.75 | 1.45 ± 0.82 | 1.09 ± 0.83 | 0.0023 |
| UPDRSII Score** | 11.36 ± 4.7 | 6.18 ± 3.6 | 4.90 ± 3.33 | 0.0036 |
| NMSS** | 22.36 ± 7.05 | 12.55 ± 5.54 | 10.36 ± 4.54 | 0.003 |
| PAC-QOL score** | 102.55 ± 5.05 | 51.27 ± 6.71 | 43.45 ± 5.34 | <0.0001 |
| Wexner constipation score* | 11.63 ± 3.22 | 8.16 ± 2.62 | 6.22 ± 1.03 | 0.0231 |
| HCY (μmol/L)** | 15.85 ± 2.89 | 12.74 ± 2.05 | 11.22 ± 1.85 | 0.002 |
| Alb (g/L) | 38.49 ± 3.92 | 40.38 ± 4.35 | 41.62 ± 4.26 | |
| UA (μmol/L) | 306.13 ± 75.94 | 282.09 ± 65.31 | 274.91 ± 55.73 | |
| OCTT (min)** | 150.91 ± 12.21 | NA | 105.45 ± 20.18 | <0.0001 |

H-Y Grade: Hoehn-Yahr Grade, UPDRS II Score: Unified Parkinson's Disease Rating Scale II Score, NMSS: non-motor symptom questionnaire, BMI: body mass index (mm/kg²), HCY: homocysteine, Alb: albumen, UA: uric acid

* p < 0.05 Before FMTvs 12 weeks After FMT in the same patient

** p < 0.01 Before FMTvs 12 weeks After FMT in the same patient

Kiitos!



Lena Brundin



Patrik Brundin



Viviane Labrie



Aoji Xie



Malú Tansey



Madelyn Houser



Knut Rudi



Jeffrey Boertien



Tuomas Mertsalmi

