The Gut in people with Cystic Fibrosis

17th November 2022

Laura Caley RD, Mres(clin), PhD student

Supervisors: Professor Daniel Peckham and Dr Helen White

Aims

UNIVERSITY OF LEEDS

1. GI symptoms
2. Basic gut physiology
3. What is the gut microbiota?
4. Is it abnormal in CF?
5. Impact of CFTR modulators?
6. How does the gut microbiota relate to colorectal cancer?

Cystic Fibrosis Trust

Aims

UNIVERSITY OF LEEDS

1. **GI symptoms**
2. Basic gut physiology
3. What is the gut microbiota?
4. Is it abnormal in CF?
5. Impact of CFTR modulators?
6. How does the gut microbiota relate to colorectal cancer?

Cystic Fibrosis Trust

GI symptoms in people with Cystic Fibrosis

UNIVERSITY OF LEEDS

Cystic Fibrosis Trust

- Flatulence
- Abdominal distension
- Reduced appetite
- Abdominal pain
- Bloating
- Acid Reflux
- DIOS
- Constipation
- Diarrhoea
- Steatorrhea

Aims

UNIVERSITY OF LEEDS

1. GI symptoms
2. **Basic gut physiology**
3. What is the gut microbiota?
4. Is it abnormal in CF?
5. Impact of CFTR modulators?
6. How does the gut microbiota relate to colorectal cancer?

Cystic Fibrosis Trust

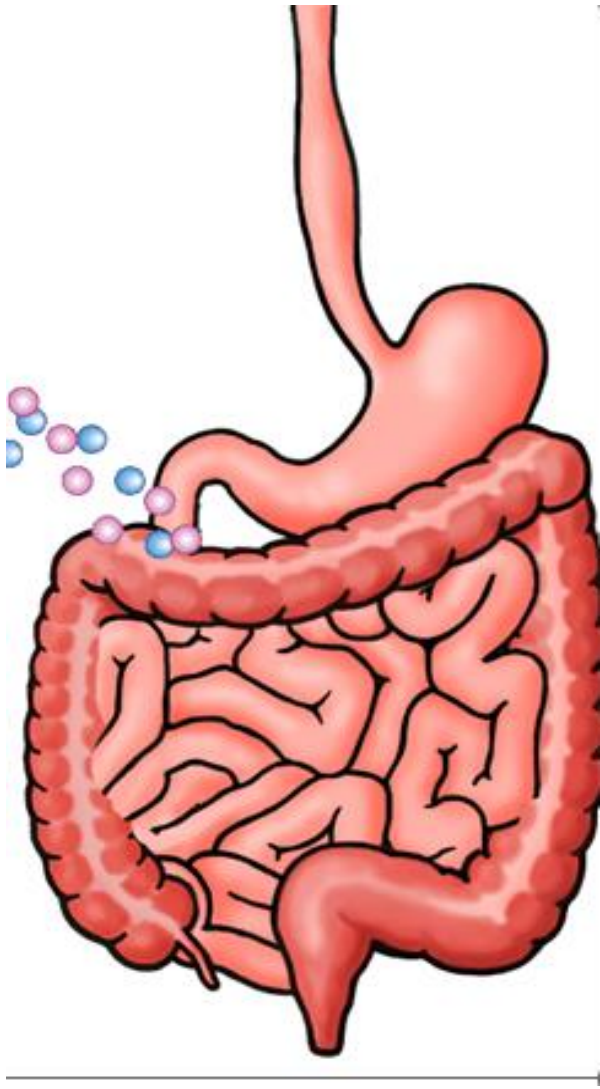
The Gut in Cystic Fibrosis

Cystic Fibrosis Trust

UNIVERSITY OF LEEDS

- Exocrine pancreatic insufficiency
- Small intestinal bacterial overgrowth
- CF-related liver disease
- Increase colon cancer risk

- Altered transit
- Altered mucus
- Intestinal inflammation
- Gut dysbiosis



Hedsund et al., 2012; Dellschaft et al., 2021; Hansson, 2019; Jaudszus et al., 2022; Burke et al., 2017; Li and Somerset, 2014; Yomada et al., 2018; Than et al., 2016; Tjalsma et al., 2012; Ullman and Itzkowitz 2011; Vieira et al., 2017; Louis et al., 2014; Mirzaei et al., 2021

Aims

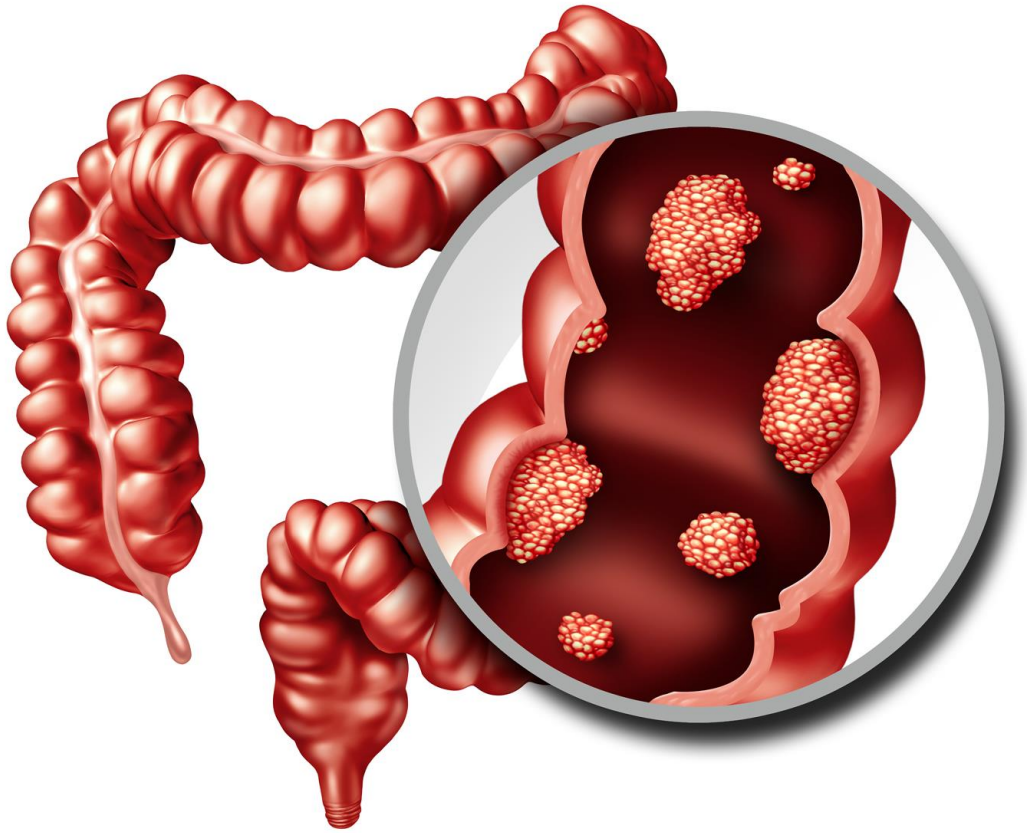
UNIVERSITY OF LEEDS

1. GI symptoms
2. Basic gut physiology
3. **What is the gut microbiota?**
4. Is it abnormal in CF?
5. Impact of CFTR modulators?
6. How does the gut microbiota relate to colorectal cancer?

Cystic Fibrosis Trust

The Gut Microbiota

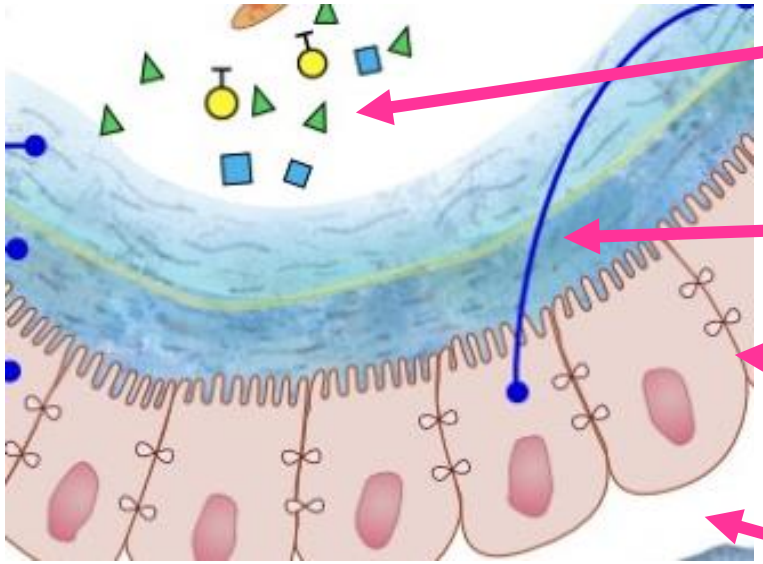
UNIVERSITY OF LEEDS



Cystic Fibrosis Trust

Gut Microbiota in Health

UNIVERSITY OF LEEDS



Bacteria and their anti-inflammatory-inducing products

Strong mucus layer

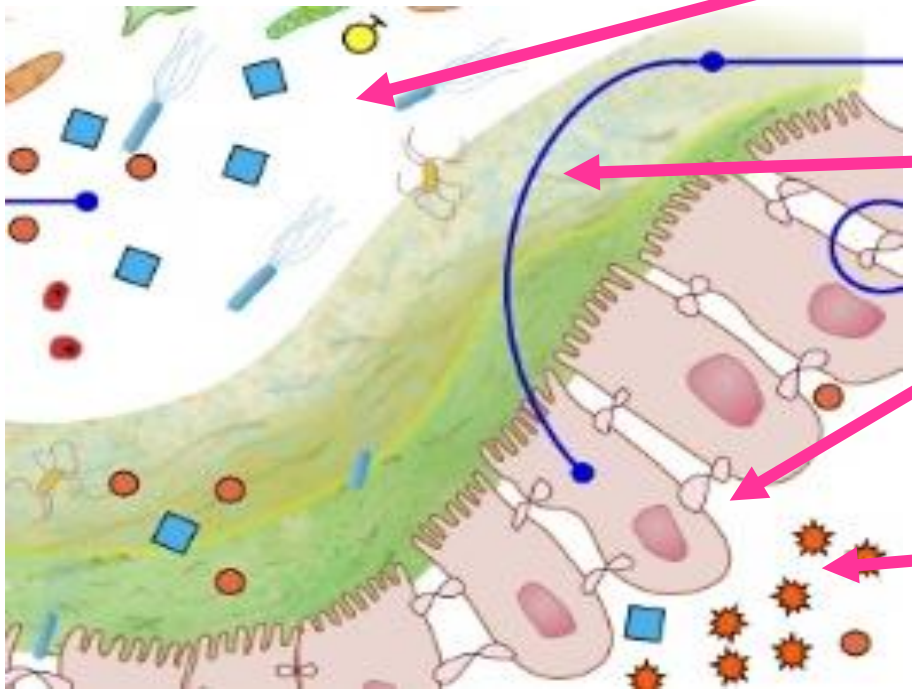
Cells lining the colon held tightly together

Bacteria does not reach the immune cells but anti-inflammatory products can so inflammation is not triggered

Trompette et al., 2018

Gut Dysbiosis

UNIVERSITY OF LEEDS



Bacteria and their inflammatory-inducing products

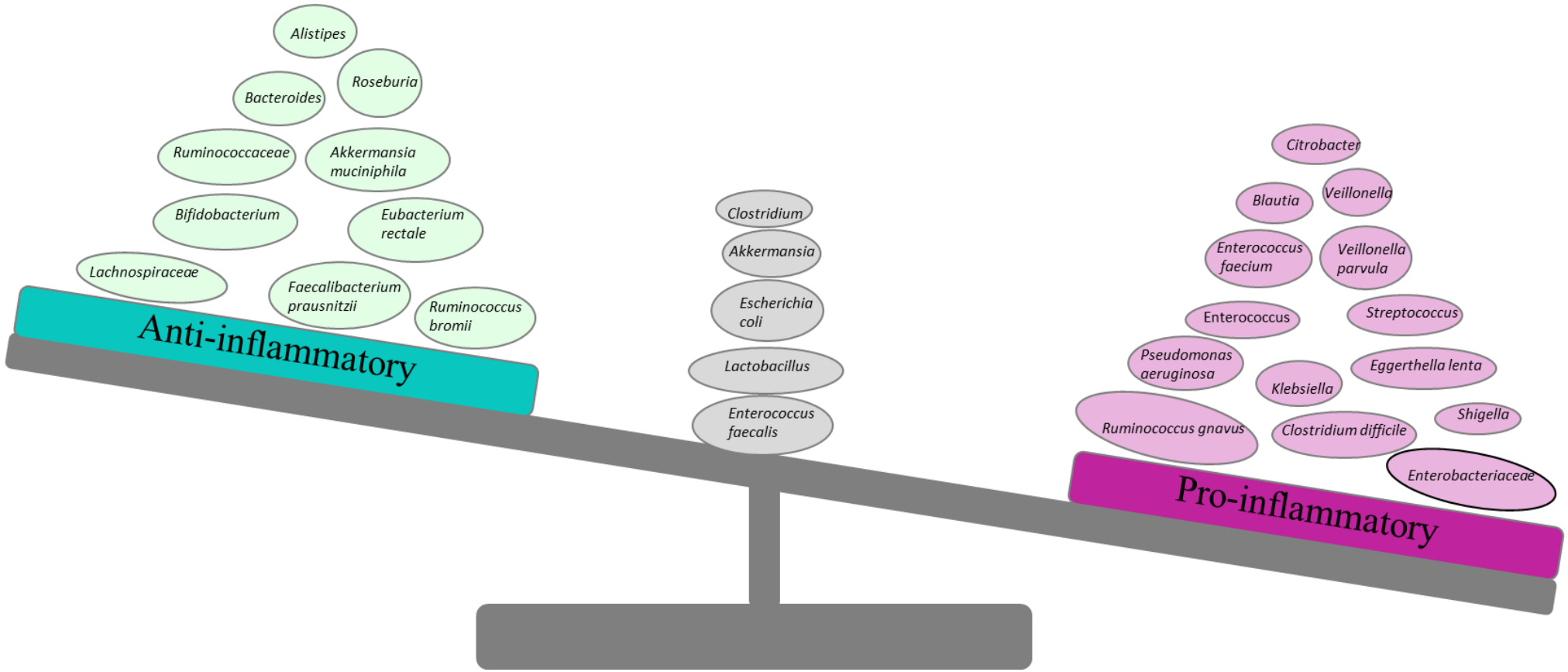
Weak mucus layer

Big gaps between cells lining the colon

Bacteria and their inflammatory-inducing products reach immune cells and trigger inflammation

Gut Dysbiosis

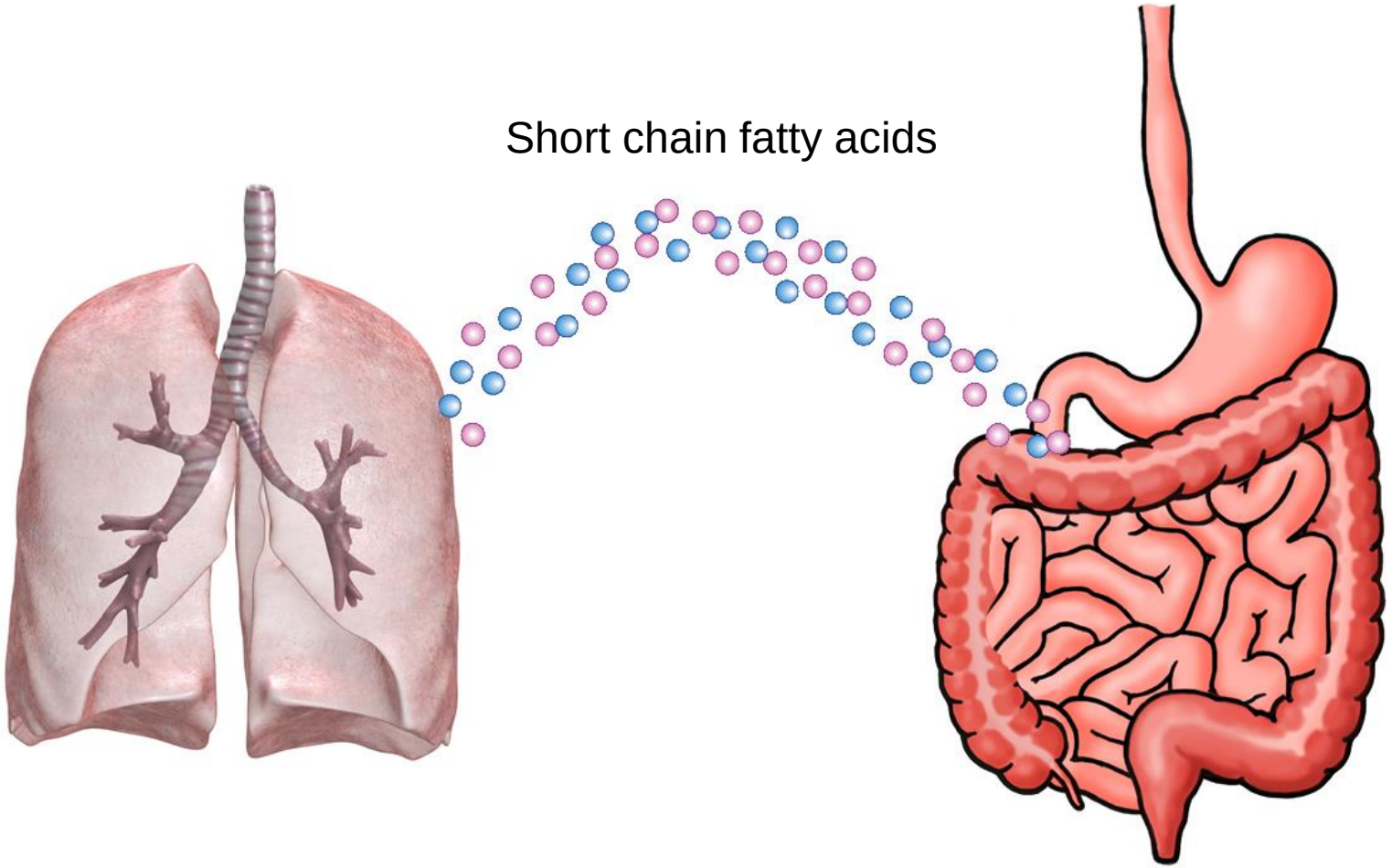
UNIVERSITY OF LEEDS



(d'Hennezel et al., 2017, Vatanen et al., 2016, Everard et al., 2013, Jiang et al., 2015, O'Callaghan and van Sinderen, 2016, Khokhlova et al., 2012, Groeger et al., 2013, Zhu et al., 2018, Wei et al., 2016, Sokol et al., 2008, Arrieta et al., 2015, Schirmer et al., 2016, Dubourg et al., 2016, Wexler, 2007, Gurung et al., 2020, Kang et al., 2017, Mukherjee et al., 2020, Coats et al., 2005, Yang and Jobin, 2014, Are et al., 2008, Wang et al., 2014, Castro et al., 2010, Molina et al., 2015, Huycke et al., 2002, Ottman et al., 2017, Zhao et al., 2017, Demirci et al., 2019, Candela et al., 2012, Nabizadeh et al., 2017, Zheng et al., 2016, Zhang et al., 2020, Rocha-Ramírez et al., 2017, Chang et al., 2008, Chia et al., 2017, Elsayed and Zhang, 2004a, Elsayed and Zhang, 2004b, Randazzo et al., 2015, Toprak et al., 2014, Lopetuso et al., 2013, Chua et al., 2018, Hall et al., 2017, Gardiner et al., 2015, Okuda et al., 2010, Zaborina et al., 2006, Gevers et al., 2014, Pustelny et al., 2015, Matera et al., 2009, Seishima et al., 2019, Wlodarska et al., 2011, National Institute for Health and Care Excellence, 2014, Kashtanova et al., 2018, Tuovinen et al., 2013, Abdulamir et al., 2011, Abdulamir et al., 2010, Ellmerich et al., 2000, Dubin and Pamer, 2014, Le Chatelier et al., 2013, Anderson et al., 2016, Sansonetti et al., 2000, Singh et al., 2016, Salem et al., 2019)

The Gut - Lung - Axis

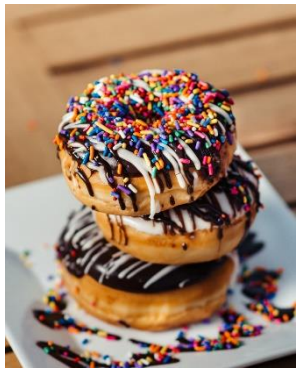
UNIVERSITY OF LEEDS



Cystic Fibrosis Trust

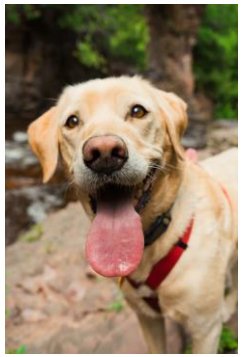
Trompette et al., 2018; Zhang et al., 2020a

Factors affecting the gut microbiota









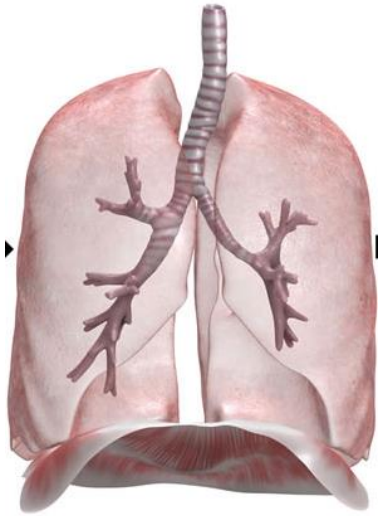


@nynnes, @rareyesphoto, @amir_v_ali, @kobbyfotos, @myriamzilles, @diana_pole, @hush52. Available at: https://unsplash.com/ @luddyphoto, @alexmotoc, @nynnes, @nynnes, @nadineprimeau, @diana_pole, @jsweissphoto, Available at: https://unsplash.com/ [date accessed: 29/01/21]

Francino, 2018; Stewart et al., 2018; van den Elsen et al., 2019; Bode, 2015, Ayechu-Muruzabal et al., 2018; He et al., 2016, Lehmann et al., 2015; Kaetzel, 2014; David et al., 2014; Anand and Mande, 2018, McRorie, 2015a, McRorie, 2015b, Kumar Singh et al., 2019, Larrosa et al., 2009, Diether and Willing, 2019, Garcia-Mantrana et al., 2018, Cani et al., 2007, Schroeder et al., 2018, Plöger et a 2012, Debray et al., 2018, Bian et al., 2017, Andriamihaja et al., 2015, Fung et al., 2013, Llewellyn et al., 2018; Monda et al., 2017; Penders et al., 2005, Stanislawski et al., 2018; Langdon et al., 2016; Bäckhed et al., 2004; Wan et al., 2020, Tidjani Alou et al., 2017; Debray et al., 2018, Hojo et al., 2018; Imhann et al., 2016; Laheij et al., 2004; Jakobsson et al., 2010, Raymond et al., 2016; Theriot e al., 2014; Kim et al., 2014; Virta et al., 2012; Korpela et al., 2016; Boursi et al., 2015; Zhang et al., 2018; Lee et al., 2018;

The Gut - Lung - Axis

UNIVERSITY OF LEEDS



Cystic Fibrosis Trust

Aims

UNIVERSITY OF LEEDS

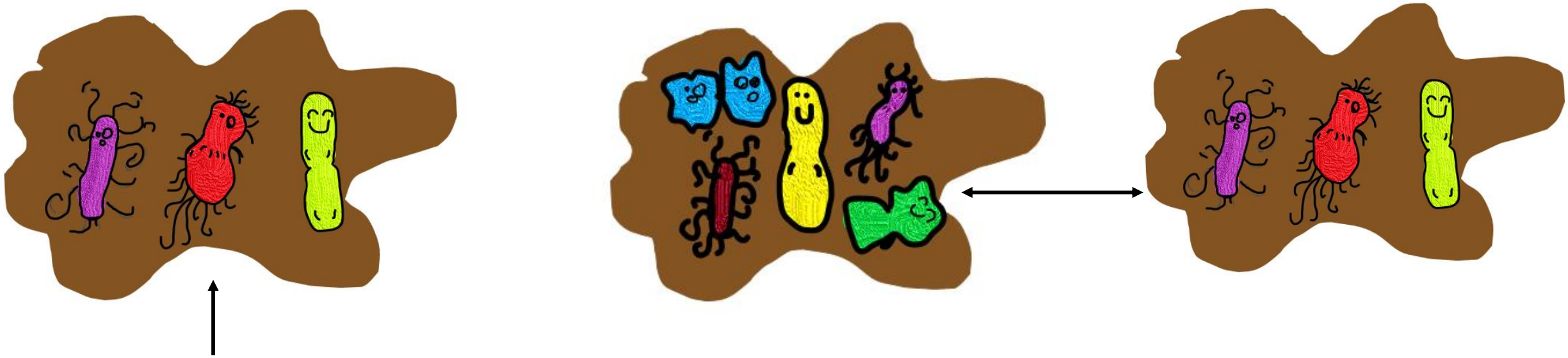
1. GI symptoms
2. Basic gut physiology
3. What is the gut microbiota?
4. **Is it abnormal in CF?**
5. Impact of CFTR modulators?
6. How does the gut microbiota relate to colorectal cancer?

Cystic Fibrosis Trust

Gut Dysbiosis and CF: Literature Review

UNIVERSITY OF LEEDS

- Diversity measures:



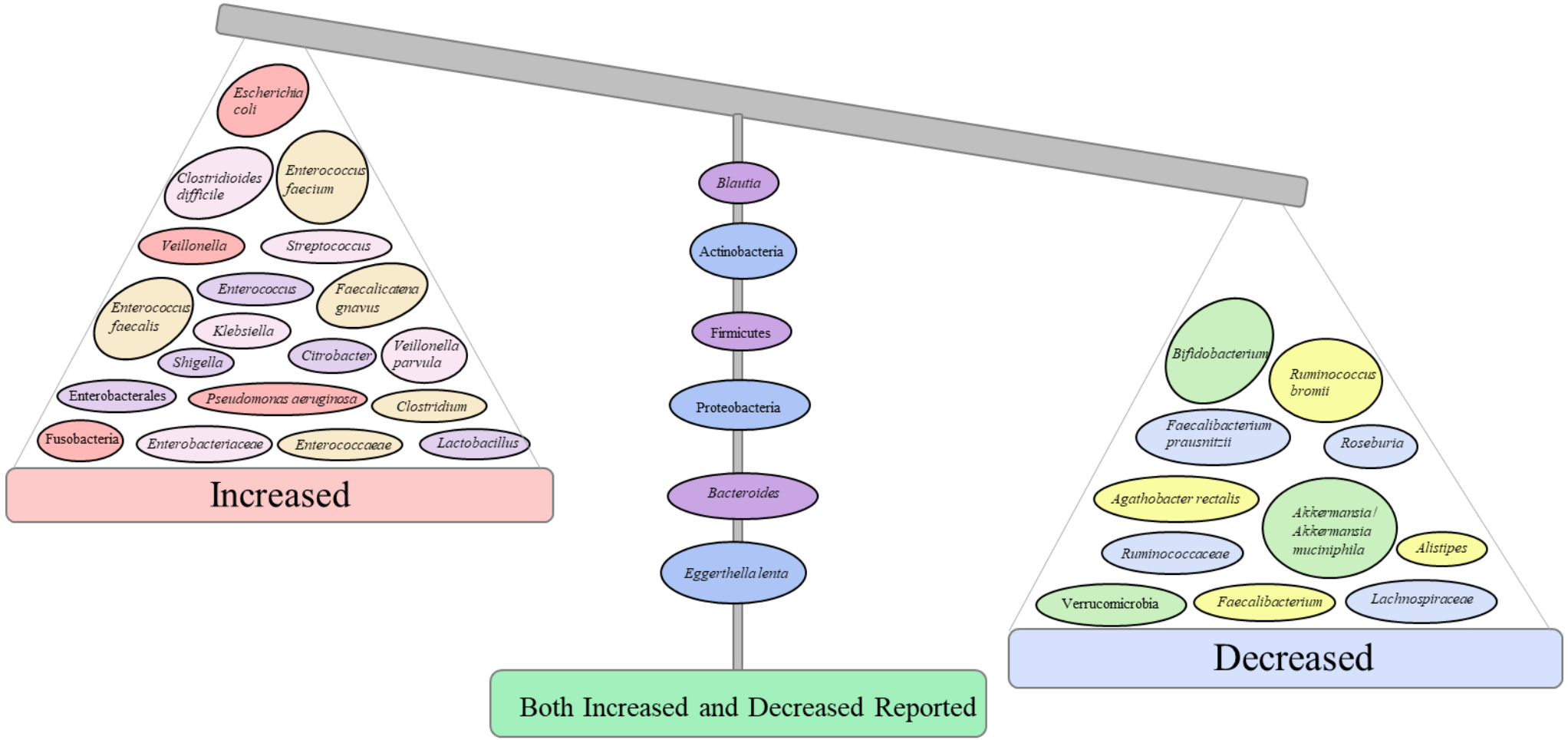
Alpha-diversity = within a sample

Beta-diversity = between samples

Antosca et al., 2019; Bruzzese et al., 2014; Burke et al., 2017; Coffey et al., 2019; Dayama et al., 2020; Debyser et al., 2016; del Campo et al., 2014; de Freitas et al., 2018; Duytschaever 2011; 2013a; 2013b; Enaud et al., 2019; Flass et al., 2015; Fouhy et al., 2017; Hayden et al., 2020; Hoffman et al., 2014; Hoen et al., 2015; Kanhere et al., 2018; Kristensen et al., 2020; 2021; Li et al., 2017; 2018; Loman et al., 2020; Madan et al., 2012; Manor et al., 2016; Matamouros et al., 2018; Miragoli et al., 2017; Nielsen et al., 2016; Ooi et al., 2018; Scalan et al., 2012; Schippa et al., 2013; Sidhu et al., 1998; Taylor et al., 2020; Van Biervliet et al., 2018; Vernocchi et al., 2017; 2018; Wang et al., 2019

Gut Dysbiosis and CF: Literature Review

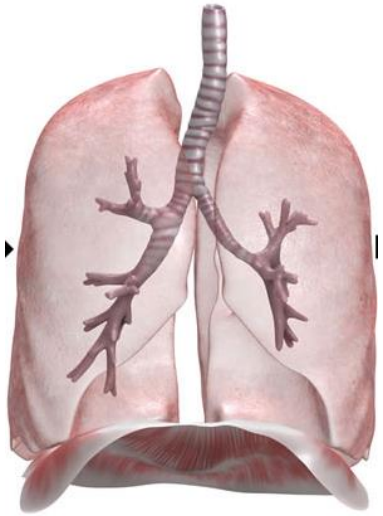
UNIVERSITY OF LEEDS



Antosca et al., 2019; Bruzzese et al., 2014; Burke et al., 2017; Coffey et al., 2019; Dayama et al., 2020; Debyser et al., 2016; del Campo et al., 2014; de Freitas et al., 2018; Duytschaever 2011; 2013a; 2013b; Enaud et al., 2019; Flass et al., 2015; Fouhy et al., 2017; Hayden et al., 2020; Hoffman et al., 2014; Hoen et al., 2015; Kanhere et al., 2018; Kristensen et al., 2020; 2021; Li et al., 2017; 2018; Loman et al., 2020; Madan et al., 2012; Manor et al., 2016; Matamouros et al., 2018; Miragoli et al., 2017; Nielsen et al., 2016; Ooi et al., 2018; Scalan et al., 2012; Schippa et al., 2013; Sidhu et al., 1998; Taylor et al., 2020; Van Biervliet et al., 2018; Vernocchi et al., 2017; 2018; Wang et al., 2019

The Gut - Lung – Axis in pwCF

UNIVERSITY OF LEEDS



Cystic Fibrosis Trust

Aims

UNIVERSITY OF LEEDS

1. GI symptoms
2. Basic gut physiology
3. What is the gut microbiota?
4. Is it abnormal in CF?
5. **Impact of CFTR modulators?**
6. How does the gut microbiota relate to colorectal cancer?

Cystic Fibrosis Trust

CFTR modulators and the CF gut

UNIVERSITY OF LEEDS

- Weight
- GI transit and pH:
    - IVA improved proximal small intestinal pH profile
    - No change in whole gut transit time with IVA
- Inflammation

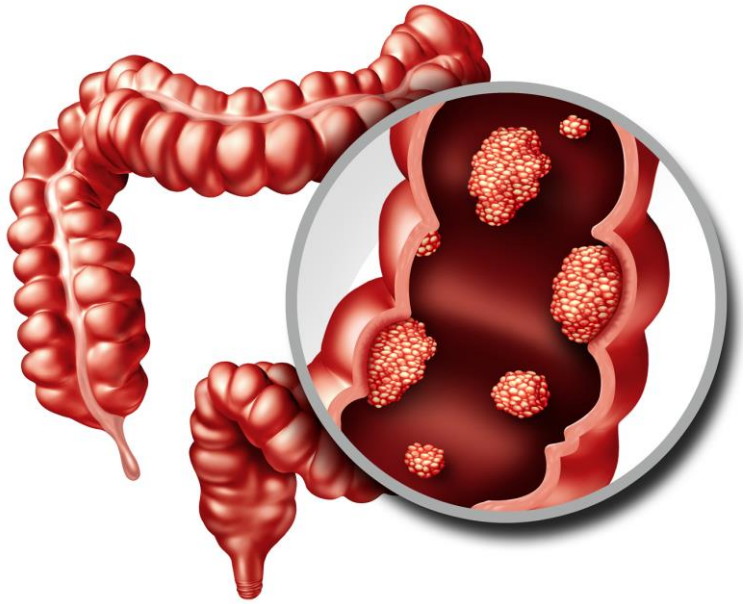
Cystic Fibrosis Trust

Szentpetery et al., 2022; Stalling et al., 2018; Gelford et al., 2017; Ooi et al., 2018; Tetard et al., 2020; Bailey et al., 2021

CFTR modulators, gut dysbiosis and CF

UNIVERSITY OF LEEDS

- Gut microbiota changes with CFTR modulator use



Cystic Fibrosis Trust

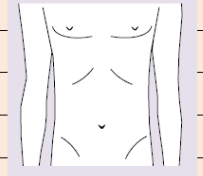
Kristensen et al., 2021; Ooi et al., 2018; Ronan et al., 2021

GI symptoms with triple therapy

UNIVERSITY OF LEEDS

- N=107 pwCF German and UK cohorts
- CFAbd-Score© pre and up to 26 weeks after commencing triple therapy compared to healthy controls

Questionnaire on abdominal symptoms and how they relate to quality of life in CF – CFAbd-Score

Please rate to what extent you have/your child has experienced the following symptoms during the past **2 weeks.**	not at all	rarely (once)	occasionally (2-3 times)	frequently (4-7 times)	almost always (on more than half the days)	always (daily)
1. Abdominal pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
If yes, where? *(please locate)*  2. Abdominal bloating	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Flatulence	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Heartburn	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Reflux of stomach content	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Nausea	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Vomiting	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Lack of appetite	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Cystic Fibrosis Trust

Mainz et al., 2022

GI symptoms with triple therapy: Mainz et al. 2022

UNIVERSITY OF LEEDS

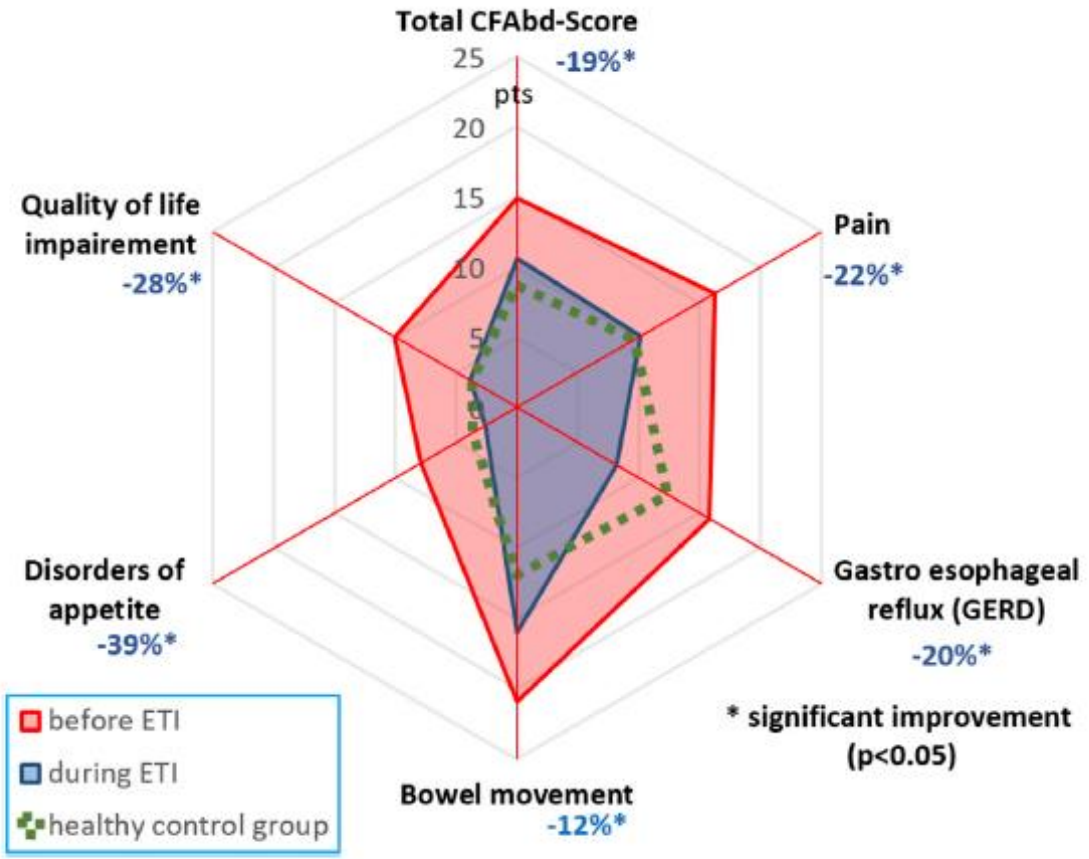


FIGURE 1 | CFAbd-Score changes for the whole cohort and its 5 domains after therapy initiation (**Table 1**). Percent changes are calculated from estimated marginal means (EMMs) at week 24 of ETI therapy.

Cystic Fibrosis Trust

GI symptoms with triple therapy: Mainz et al. 2022

UNIVERSITY OF LEEDS

- Differences in UK and German cohorts:
- German cohort highly significant decrease in total CFAbd-Score
- UK cohort not statistically significant decrease in total CFAbd-Score
- Potential reasons:
    - German cohort : 12+ years (5% PS, rest PI)
    - UK cohort PI adults only
    - Diet?
    - UK cohort where on modulators longer time

Cystic Fibrosis Trust

GI symptoms with triple therapy: Schwarzenberg et al., 2022

UNIVERSITY OF LEEDS

- United States aged ≥ 12 years old
- GI questionnaires data n=438:
    - Patient Assessment of Upper Gastrointestinal Disorders-Symptom severity Index [PAGI-SYM]
    - Patient Assessment of Constipation-Symptom Severity Index [PAC-SYM]
    - Patient Assessment of Constipation Quality of Life [PAC QOL])
    - Stool-specific questionnaire (SSQ)
- N=137 one or more of the following:
    - faecal calprotectin,
    - steatocrit (measuring fat in stool)
    - pancreatic elastase-1

Cystic Fibrosis Trust

Schwarzenberg et al., 2022

	N	Adjusted Change (95% Confidence Interval)
PAGI-SYM Total Score	**263**	**-0.15 (-0.21, -0.09)**
Nausea/Vomiting		-0.14 (-0.21, -0.07)
Fullness/Early Satiety		-0.17 (-0.27, -0.07)
Bloating		0.02 (-0.10, 0.14)
Upper Abdominal Pain		-0.19 (-0.28, -0.09)
Lower Abdominal Pain		-0.25 (-0.35, -0.16)
Heartburn/Regurgitation		-0.17 (-0.24, -0.11)
PAC-SYM Total Score	**267**	**-0.14 (-0.19, -0.09)**
Abdominal Symptoms		-0.19 (-0.27, -0.12)
Rectal Symptoms		-0.03 (-0.08, 0.02)
Stool Symptoms		-0.16 (-0.22, -0.09)
PAC-QOL Total Score	**256**	**-0.15 (-0.21, -0.10)**
Physical Discomfort		-0.11 (-0.18, -0.04)
Psychosocial Discomfort		-0.15 (-0.21, -0.09)
Worries and Concerns		-0.14 (-0.21, -0.08)
Dissatisfaction		-0.22 (-0.31, -0.12)

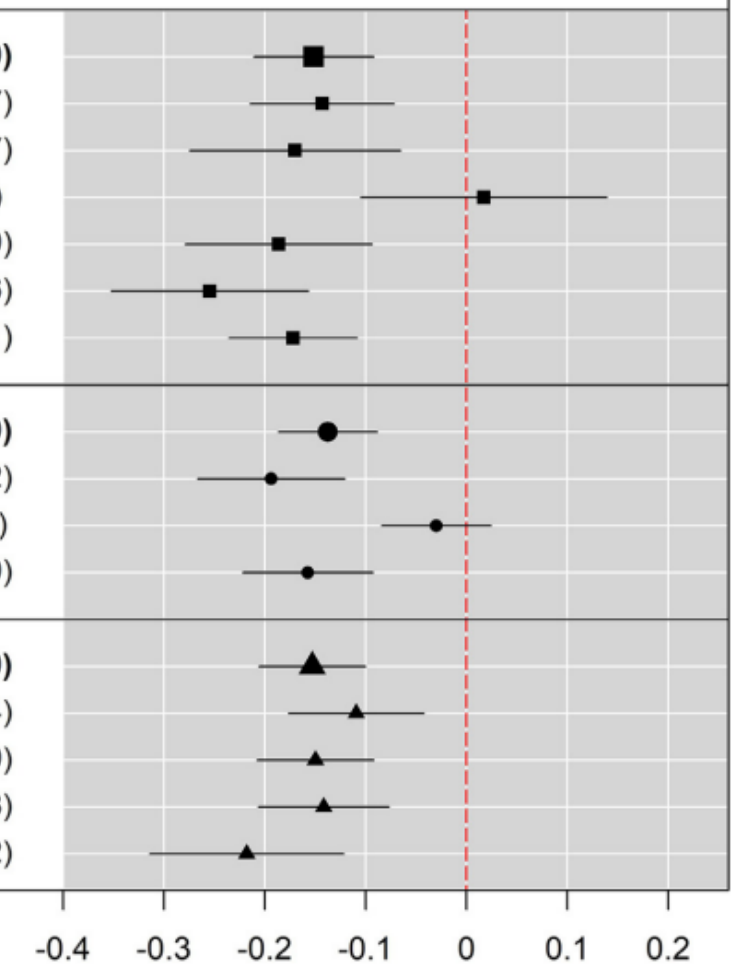


Fig. 1. Changes in PAGI-SYM, PAC-SYM, and PAC-QOL scores at 6 months Changes from baseline in total and domain scores for PAGI-SYM, PAC-SYM, and PAC-QOL at 6 months were evaluated in linear regression models with adjustments for age group at enrollment and sex at birth. Positive value of adjusted change indicates lower score (symptom improvement) at 6 months compared to baseline.

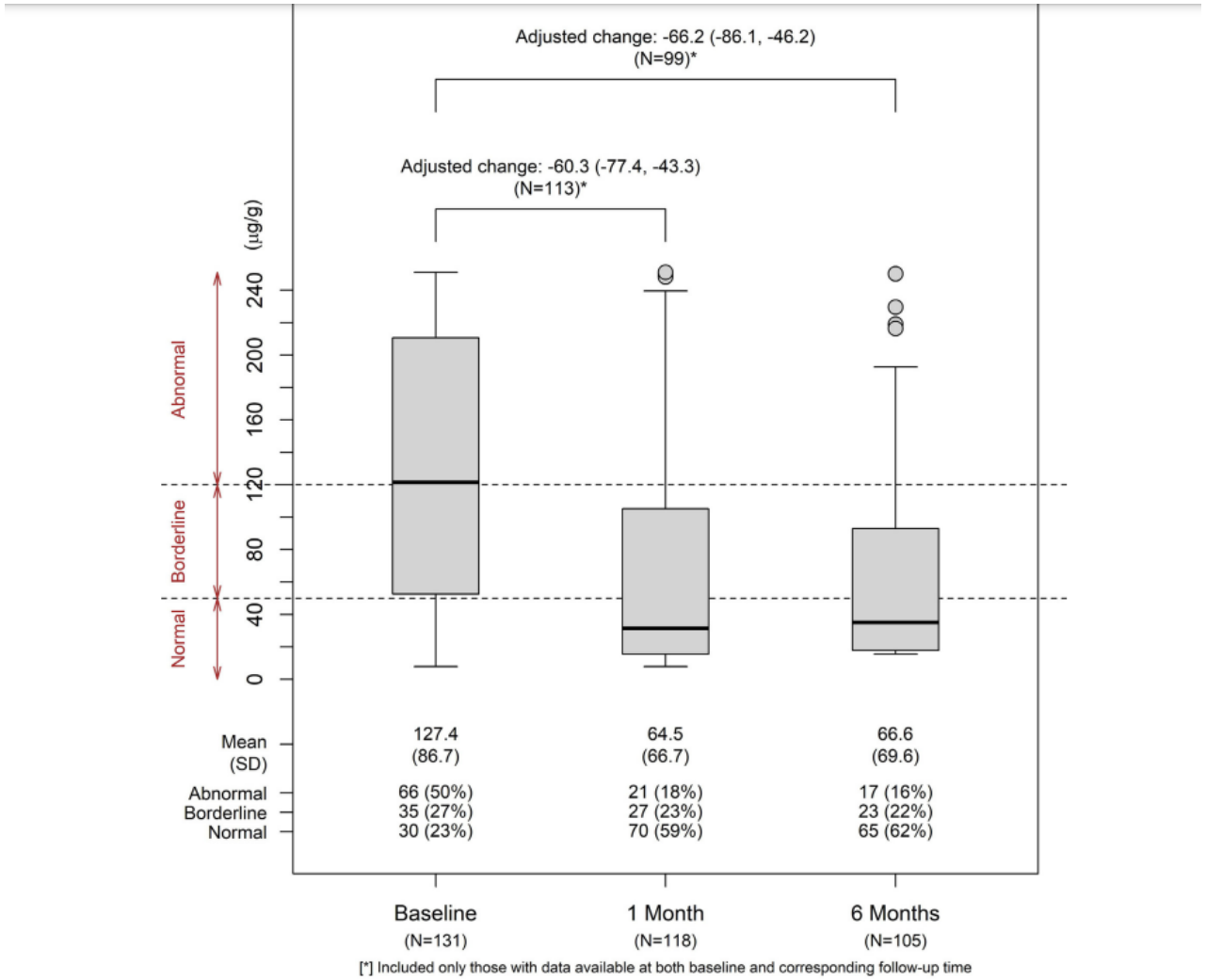


Fig. 2. Distributions of fecal calprotectin at baseline, 1 month, and 6 months Distributions of fecal calprotectin (µg/g) were summarized for visits at baseline, 1 month, and 6 months. Changes from baseline at follow-up visits were evaluated in linear regression models with adjustments for age group at enrollment, sex at birth, and prior modulator use, among participants who had available data at both baseline and the corresponding follow-up visits (N=113 at 1 month and N=99 at 6 months).

Cystic Fibrosis Trust

Schwarzenberg et al., 2022

GI symptoms with triple therapy: Schwarzenberg et al., 2022

UNIVERSITY OF LEEDS

- Six months ETI therapy:
- PAGI-GYM bloating and PAC-Sym rectal symptoms non-statistically significantly increased
- All other domains significantly decreased

    - but not by the Minimal Clinically Important Difference (MCID)

- Faecal calprotectin levels decreased with ETI therapy
- No significant change in steatocrit (or pancreatic elastase-1 after six months of ETI therapy, indicating EPI did not improve in this group

Cystic Fibrosis Trust

Igloo-CF Study

UNIVERSITY OF LEEDS

Observation cohort study in adults with CF investigating links between the:

- Gut microbiota
- SCFA levels
- GI symptoms
- Dietary intake
- Gut-Lung-Axis
- Changes in above parameters with CFTR modulators

Results due shortly!

Cystic Fibrosis Trust

Aims

UNIVERSITY OF LEEDS

1. GI symptoms
2. Basic gut physiology
3. What is the gut microbiota?
4. Is it abnormal in CF?
5. Impact of CFTR modulators?
6. **How does the gut microbiota relate to colorectal cancer?**

Cystic Fibrosis Trust

The gut microbiota in pwCF compared to those with colorectal cancer

UNIVERSITY OF LEEDS

- Gut Microbiota and Colorectal Cancer

Original Article

The risk of colorectal cancer in individuals with mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene: An English population-based study

Rebecca J. Birch[a,b,*], Daniel Peckham[a,c], Henry M. Wood[a], Philip Quirke[a], Rob Konstant-Hambling[d], Keith Brownlee[e], Rebecca Cosgriff[f], Genomics England Research Consortium[5,#], Nicholas Burr[g], Amy Downing[a,b]

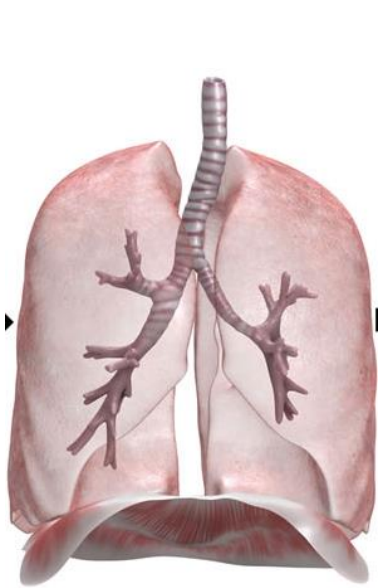
[a] *Leeds Institute of Medical Research at St James's, University of Leeds*
[b] *Leeds Institute for Data Analytics, University of Leeds*
[c] *Leeds Teaching Hospitals NHS Trust*
[d] *NHS England*
[e] *Cystic Fibrosis Trust, London, UK*
[g] *Mid Yorkshire NHS Trust*

Cystic Fibrosis Trust

Young et al., 2021a; 2021b

The Gut - Lung – Axis: Time to Change?

UNIVERSITY OF LEEDS



Cystic Fibrosis Trust

ARTICLE IN PRESS

JID: JCF [m5G;August 12, 2022;15:45]

Journal of Cystic Fibrosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Editorial

Time to change course and tackle CF related obesity

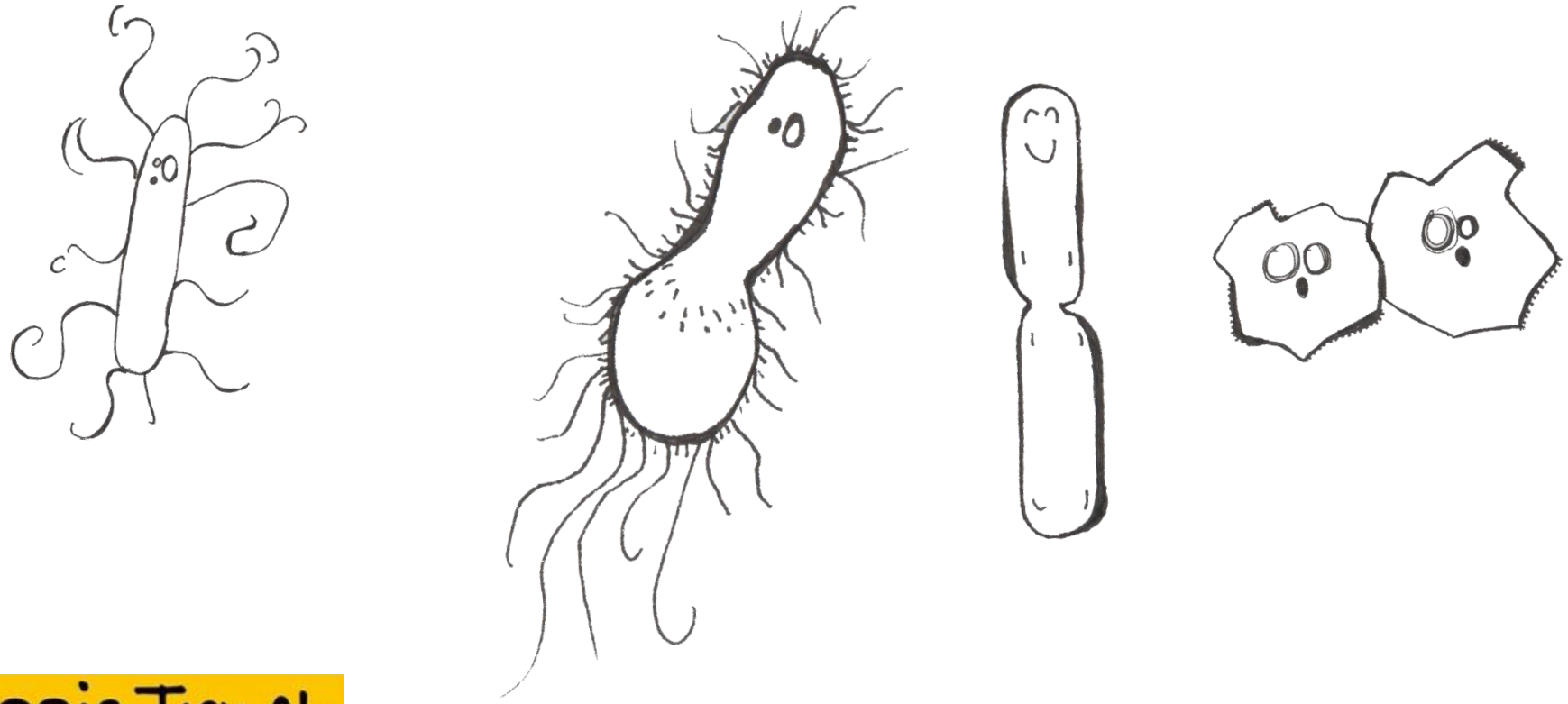
Laura Caley[a], Daniel Peckham[a,b,*]

[a] Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, United Kingdom
[b] Leeds Adult Cystic Fibrosis Unit, St James's University Hospital, Leeds, United Kingdom

'So how should we readjust nutritional care in this rapidly changing landscape? Just as Crozier's work radically changed dietary care, and contrasted with the prevailing clinical view, the CF community should consider another radical change to improve lifespan beyond previous expectations'

UNIVERSITY OF LEEDS

Thanks to Professor Daniel Peckham, Dr Helen White, the CF Trust, SRC 012 team, Professor Phil Quirke, our study participants and to you all for listening



Cystic Fibrosis Trust

UNIVERSITY OF LEEDS

Thank you for listening

Questions welcome

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- ABDULAMIR, A. S., HAFIDH, R. R. & BAKAR, F. A. 2010. Molecular detection, quantification, and isolation of Streptococcus gallolyticus bacteria colonizing colorectal tumors: inflammation-driven potential of carcinogenesis via IL-1, COX-2, and IL-8. *Mol Cancer,* 9**,** 249.
- ABDULAMIR, A. S., HAFIDH, R. R. & BAKAR, F. A. 2011. The association of Streptococcus bovis/gallolyticus with colorectal tumors: The nature and the underlying mechanisms of its etiological role. *Journal of Experimental & Clinical Cancer Research,* 30**,** 11.
- ANAND, S. & MANDE, S. S. 2018. Diet, Microbiota and Gut-Lung Connection. *Front Microbiol,* 9**,** 2147.
- ANDERSON, M., SANSONETTI, P. J. & MARTEYN, B. S. 2016. Shigella Diversity and Changing Landscape: Insights for the Twenty-First Century. *Frontiers in cellular and infection microbiology,* 6**,** 45-45.
- ANDRIAMIHAJA, M., LAN, A., BEAUMONT, M., AUDEBERT, M., WONG, X., YAMADA, K., YIN, Y., TOMÉ, D., CARRASCO-POZO, C., GOTTELAND, M., KONG, X. & BLACHIER, F. 2015. The deleterious metabolic and genotoxic effects of the bacterial metabolite p-cresol on colonic epithelial cells. *Free Radic Biol Med,* 85**,** 219-27.
- ARE, A., ARONSSON, L., WANG, S., GREICIUS, G., LEE, Y. K., GUSTAFSSON, J. A., PETTERSSON, S. & ARULAMPALAM, V. 2008. Enterococcus faecalis from newborn babies regulate endogenous PPARgamma activity and IL-10 levels in colonic epithelial cells. *Proc Natl Acad Sci U S A,* 105**,** 1943-8.
- ARRIETA, M. C., STIEMSMA, L. T., DIMITRIU, P. A., THORSON, L., RUSSELL, S., YURIST-DOUTSCH, S., KUZELJEVIC, B., GOLD, M. J., BRITTON, H. M., LEFEBVRE, D. L., SUBBARAO, P., MANDHANE, P., BECKER, A., MCNAGNY, K. M., SEARS, M. R., KOLLMANN, T., MOHN, W. W., TURVEY, S. E. & FINLAY, B. B. 2015. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med,* 7**,** 307ra152.
- AYECHU-MURUZABAL, V., VAN STIGT, A. H., MANK, M., WILLEMSEN, L. E. M., STAHL, B., GARSSEN, J. & VAN'T LAND, B. 2018. Diversity of Human Milk Oligosaccharides and Effects on Early Life Immune Development. *Front Pediatr,* 6**,** 239.
- BÄCKHED, F., DING, H., WANG, T., HOOPER, L. V., KOH, G. Y., NAGY, A., SEMENKOVICH, C. F. & GORDON, J. I. 2004. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A,* 101**,** 15718-23.
- BAILEY, J., ROZGA, M., MCDONALD, C. M., BOWSER, E. K., FARNHAM, K., MANGUS, M., PADULA, L., PORCO, K. & ALVAREZ, J. A. 2021. Effect of CFTR Modulators on Anthropometric Parameters in Individuals with Cystic Fibrosis: An Evidence Analysis Center Systematic Review. *J Acad Nutr Diet,* 121**,** 1364-1378.e2.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- BIAN, X., CHI, L., GAO, B., TU, P., RU, H. & LU, K. 2017. Gut Microbiome Response to Sucralose and Its Potential Role in Inducing Liver Inflammation in Mice. *Front Physiol,* 8**,** 487.
- BIRCH, R. J., PECKHAM, D., WOOD, H. M., QUIRKE, P., KONSTANT-HAMBLING, R., BROWNLEE, K., COSGRIFF, R., CONSORTIUM, G. E. R., BURR, N. & DOWNING, A. 2022. The risk of colorectal cancer in individuals with mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene: An English population-based study. *J Cyst Fibros*.
- BODE, L. 2015. The functional biology of human milk oligosaccharides. *Early Hum Dev,* 91**,** 619-22.
- BOURSI, B., MAMTANI, R., HAYNES, K. & YANG, Y. X. 2015. The effect of past antibiotic exposure on diabetes risk. *Eur J Endocrinol,* 172**,** 639-48.
- BRUZZESE, E., CALLEGARI, M. L., RAIA, V., VISCOVO, S., SCOTTO, R., FERRARI, S., MORELLI, L., BUCCIGROSSI, V., LO VECCHIO, A., RUBERTO, E. & GUARINO, A. 2014. Disrupted intestinal microbiota and intestinal inflammation in children with cystic fibrosis and its restoration with Lactobacillus GG: a randomised clinical trial. *PLoS One,* 9**,** e87796.
- BURKE, D. G., FOUHY, F., HARRISON, M. J., REA, M. C., COTTER, P. D., O'SULLIVAN, O., STANTON, C., HILL, C., SHANAHAN, F., PLANT, B. J. & ROSS, R. P. 2017. The altered gut microbiota in adults with cystic fibrosis. *BMC Microbiol,* 17**,** 58.
- CAIT, A., HUGHES, M. R., ANTIGNANO, F., CAIT, J., DIMITRIU, P. A., MAAS, K. R., REYNOLDS, L. A., HACKER, L., MOHR, J., FINLAY, B. B., ZAPH, C., MCNAGNY, K. M. & MOHN, W. W. 2018. Microbiome-driven allergic lung inflammation is ameliorated by short-chain fatty acids. *Mucosal Immunol,* 11**,** 785-795.
- CALEY, L., SMITH, L., WHITE, H. & PECKHAM, D. G. 2021. Average rate of lung function decline in adults with cystic fibrosis in the United Kingdom: Data from the UK CF registry. *J Cyst Fibros,* 20**,** 86-90.
- CALEY, L. & PECKHAM, D. 2022. Time to change course and tackle CF related obesity. *J Cyst Fibros*.
- CANDELA, M., RAMPELLI, S., TURRONI, S., SEVERGNINI, M., CONSOLANDI, C., DE BELLIS, G., MASETTI, R., RICCI, G., PESSION, A. & BRIGIDI, P. 2012. Unbalance of intestinal microbiota in atopic children. *BMC Microbiology,* 12**,** 95.
- CANI, P. D., AMAR, J., IGLESIAS, M. A., POGGI, M., KNAUF, C., BASTELICA, D., NEYRINCK, A. M., FAVA, F., TUOHY, K. M., CHABO, C., WAGET, A., DELMÉE, E., COUSIN, B., SULPICE, T., CHAMONTIN, B., FERRIÈRES, J., TANTI, J.-F., GIBSON, G. R., CASTEILLA, L., DELZENNE, N. M., ALESSI, M. C. & BURCELIN, R. 2007. Metabolic Endotoxemia Initiates Obesity and Insulin Resistance. *Diabetes,* 56**,** 1761.
- CASÉN, C., VEBØ, H. C., SEKELJA, M., HEGGE, F. T., KARLSSON, M. K., CIEMNIEJEWSKA, E., DZANKOVIC, S., FRØYLAND, C., NESTESTOG, R., ENGSTRAND, L., MUNKHOLM, P., NIELSEN, O. H., ROGLER, G., SIMRÉN, M., ÖHMAN, L., VATN, M. H. & RUDI, K. 2015. Deviations in human gut microbiota: a novel diagn ermining dysbiosis in patients with IBS or IBD. *Aliment Pharmacol Ther,* 42**,** 71-83.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- CASTRO, M. S., MOLINA, M. A., DI SCIULLO, P., AZPIROZ, M. B., LEOCATA NIETO, F., STERÍN-SPEZIALE, N. B., MONGINI, C. & MANGHI, M. A. 2010. Beneficial activity of Enterococcus faecalis CECT7121 in the anti-lymphoma protective response. *J Appl Microbiol,* 109**,** 1234-43.
- CHAABAN, M. R., KEJNER, A., ROWE, S. M. & WOODWORTH, B. A. 2013. Cystic fibrosis chronic rhinosinusitis: a comprehensive review. *Am J Rhinol Allergy,* 27**,** 387-95.
- CHANG, J. Y., ANTONOPOULOS, D. A., KALRA, A., TONELLI, A., KHALIFE, W. T., SCHMIDT, T. M. & YOUNG, V. B. 2008. Decreased diversity of the fecal Microbiome in recurrent Clostridium difficile-associated diarrhea. *J Infect Dis,* 197**,** 435-8.
- CHIA, J. H., FENG, Y., SU, L. H., WU, T. L., CHEN, C. L., LIANG, Y. H. & CHIU, C. H. 2017. Clostridium innocuum is a significant vancomycin-resistant pathogen for extraintestinal clostridial infection. *Clin Microbiol Infect,* 23**,** 560-566.
- CHUA, H. H., CHOU, H. C., TUNG, Y. L., CHIANG, B. L., LIAO, C. C., LIU, H. H. & NI, Y. H. 2018. Intestinal Dysbiosis Featuring Abundance of Ruminococcus gnavus Associates With Allergic Diseases in Infants. *Gastroenterology,* 154**,** 154-167.
- COATS, S. R., PHAM, T. T., BAINBRIDGE, B. W., REIFE, R. A. & DARVEAU, R. P. 2005. MD-2 mediates the ability of tetra-acylated and penta-acylated lipopolysaccharides to antagonize Escherichia coli lipopolysaccharide at the TLR4 signaling complex. *J Immunol,* 175**,** 4490-8.
- COFFEY, M. J., NIELSEN, S., WEMHEUER, B., KAAKOUSH, N. O., GARG, M., NEEDHAM, B., PICKFORD, R., JAFFE, A., THOMAS, T. & OOI, C. Y. 2019. Gut Microbiota in Children With Cystic Fibrosis: A Taxonomic and Functional Dysbiosis. *Sci Rep,* 9**,** 18593.
- CYSTIC FIBROSIS TRUST. 2018. *UK Cystic Fibrosis Registry 2017 Annual Data Report* [Online]. Available: https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources [Accessed 27th March 2019].
- DELLSCHAFT, N. S., NG, C., HOAD, C., MARCIANI, L., SPILLER, R., STEWART, I., MENYS, A., BARR, H., GOWLAND, P. A., MAJOR, G. & SMYTH, A. R. 2021. Magnetic resonance imaging of the gastrointestinal tract shows reduced small bowel motility and altered chyme in cystic fibrosis compared to controls. *J Cyst Fibros*.
- D'HENNEZEL, E., ABUBUCKER, S., MURPHY, L. O. & CULLEN, T. W. 2017. Total Lipopolysaccharide from the Human Gut Microbiome Silences Toll-Like Receptor Signaling. *mSystems,* 2.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- DAVID, L. A., MAURICE, C. F., CARMODY, R. N., GOOTENBERG, D. B., BUTTON, J. E., WOLFE, B. E., LING, A. V., DEVLIN, A. S., VARMA, Y., FISCHBACH, M. A., BIDDINGER, S. B., DUTTON, R. J. & TURNBAUGH, P. J. 2014. Diet rapidly and reproducibly alters the human gut microbiome. *Nature,* 505**,** 559-63.
- DE FREITAS, M. B., MOREIRA, E. A. M., TOMIO, C., MORENO, Y. M. F., DALTOE, F. P., BARBOSA, E., NETO, N. L., BUCCIGROSSI, V. & GUARINO, A. 2018. Altered intestinal microbiota composition, antibiotic therapy and intestinal inflammation in children and adolescents with cystic fibrosis. *PLoS ONE,* 13 (6) (no pagination).
- DEBRAY, D., EL MOURABIT, H., MERABTENE, F., BROT, L., ULVELING, D., CHRETIEN, Y., RAINTEAU, D., MOSZER, I., WENDUM, D., SOKOL, H. & HOUSSET, C. 2018. Diet-Induced Dysbiosis and Genetic Background Synergize With Cystic Fibrosis Transmembrane Conductance Regulator Deficiency to Promote Cholangiopathy in Mice. *Hepatol Commun,* 2**,** 1533-1549.
- DEMIRCI, M., TOKMAN, H. B., UYSAL, H. K., DEMIRYAS, S., KARAKULLUKCU, A., SARIBAS, S., COKUGRAS, H. & KOCAZEYBEK, B. S. 2019. Reduced Akkermansia muciniphila and Faecalibacterium prausnitzii levels in the gut microbiota of children with allergic asthma. *Allergol Immunopathol (Madr),* 47**,** 365-371.
- DIETHER, N. E. & WILLING, B. P. 2019. Microbial Fermentation of Dietary Protein: An Important Factor in Diet⁻Microbe⁻Host Interaction. *Microorganisms,* 7**,** 19.
- DUBIN, K. & PAMER, E. G. 2014. Enterococci and Their Interactions with the Intestinal Microbiome. *Microbiol Spectr,* 5.
- DUBOURG, G., LAGIER, J.-C., HÜE, S., SURENAUD, M., BACHAR, D., ROBERT, C., MICHELLE, C., RAVAUX, I., MOKHTARI, S., MILLION, M., STEIN, A., BROUQUI, P., LEVY, Y. & RAOULT, D. 2016. Gut microbiota associated with HIV infection is significantly enriched in bacteria tolerant to oxygen. *BMJ open gastroenterology,* 3**,** e000080-e000080.
- ELLMERICH, S., SCHÖLLER, M., DURANTON, B., GOSSÉ, F., GALLUSER, M., KLEIN, J. P. & RAUL, F. 2000. Promotion of intestinal carcinogenesis by Streptococcus bovis. *Carcinogenesis,* 21**,** 753-6.
- ELSAYED, S. & ZHANG, K. 2004a. Bacteremia caused by Clostridium symbiosum. *Journal of clinical microbiology,* 42**,** 4390-4392.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- ELSAYED, S. & ZHANG, K. 2004b. Human infection caused by Clostridium hathewayi. *Emerg Infect Dis,* 10**,** 1950-2.
- EVERARD, A., BELZER, C., GEURTS, L., OUWERKERK, J. P., DRUART, C., BINDELS, L. B., GUIOT, Y., DERRIEN, M., MUCCIOLI, G. G., DELZENNE, N. M., DE VOS, W. M. & CANI, P. D. 2013. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proceedings of the National Academy of Sciences,* 110**,** 9066.
- FRANCINO, M. P. 2018. Birth Mode-Related Differences in Gut Microbiota Colonization and Immune System Development. *Annals of Nutrition and Metabolism,* 73(suppl 3)**,** 12-16.
- FUNG, K. Y., OOI, C. C., ZUCKER, M. H., LOCKETT, T., WILLIAMS, D. B., COSGROVE, L. J. & TOPPING, D. L. 2013. Colorectal carcinogenesis: a cellular response to sustained risk environment. *Int J Mol Sci,* 14**,** 13525-41.
- GARCIA-MANTRANA, I., SELMA-ROYO, M., ALCANTARA, C. & COLLADO, M. C. 2018. Shifts on Gut Microbiota Associated to Mediterranean Diet Adherence and Specific Dietary Intakes on General Adult Population. *Frontiers in microbiology,* 9**,** 890-890.
- GARDINER, B. J., TAI, A. Y., KOTSANAS, D., FRANCIS, M. J., ROBERTS, S. A., BALLARD, S. A., JUNCKERSTORFF, R. K. & KORMAN, T. M. 2015. Clinical and Microbiological Characteristics of Eggerthella lenta Bacteremia. *Journal of Clinical Microbiology,* 53**,** 626.
- GELFOND, D., HELTSHE, S., MA, C., ROWE, S. M., FREDERICK, C., ULUER, A., SICILIAN, L., KONSTAN, M., TULLIS, E., ROACH, R. N., GRIFFIN, K., JOSELOFF, E. & BOROWITZ, D. 2017. Impact of CFTR Modulation on Intestinal pH, Motility, and Clinical Outcomes in Patients With Cystic Fibrosis and the G551D Mutation. *Clin Transl Gastroenterol,* 8**,** e81.
- GEVERS, D., KUGATHASAN, S., DENSON, L. A., VÁZQUEZ-BAEZA, Y., VAN TREUREN, W., REN, B., SCHWAGER, E., KNIGHTS, D., SONG, S. J., YASSOUR, M., MORGAN, X. C., KOSTIC, A. D., LUO, C., GONZÁLEZ, A., MCDONALD, D., HABERMAN, Y., WALTERS, T., BAKER, S., ROSH, J., STEPHENS, M., HEYMAN, M., MARKOWITZ, J., BALDASSANO, R., GRIFFITHS, A., SYLVESTER, F., MACK, D., KIM, S., CRANDALL, W., HYAMS, J., HUTTENHOWER, C., KNIGHT, R. & XAVIER, R. J. 2014. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe,* 15**,** 382-392.
- GROEGER, D., O'MAHONY, L., MURPHY, E. F., BOURKE, J. F., DINAN, T. G., KIELY, B., SHANAHAN, F. & QUIGLEY, E. M. 2013. Bifidobacterium infantis 35624 modulates host inflammatory processes beyond the gut. *Gut Microbes,* 4**,** 325-39.
- GURUNG, M., LI, Z., YOU, H., RODRIGUES, R., JUMP, D. B., MORGUN, A. & SHULZHENKO, N. 2020. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine,* 51**,** 102590.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- HALL, A. B., YASSOUR, M., SAUK, J., GARNER, A., JIANG, X., ARTHUR, T., LAGOUDAS, G. K., VATANEN, T., FORNELOS, N., WILSON, R., BERTHA, M., COHEN, M., GARBER, J., KHALILI, H., GEVERS, D., ANANTHAKRISHNAN, A. N., KUGATHASAN, S., LANDER, E. S., BLAINEY, P., VLAMAKIS, H., XAVIER, R. J. & HUTTENHOWER, C. 2017. A novel Ruminococcus gnavus clade enriched in inflammatory bowel disease patients. *Genome Med,* 9**,** 103.
- HANSSON, G. C. 2019. Mucus and mucins in diseases of the intestinal and respiratory tracts. *Journal of Internal Medicine,* 285**,** 479-490.
- HE, Y., LAWLOR, N. T. & NEWBURG, D. S. 2016. Human Milk Components Modulate Toll-Like Receptor-Mediated Inflammation. *Adv Nutr,* 7**,** 102-11.
- HEDSUND, C., GREGERSEN, T., JOENSSON, I. M., OLESEN, H. V. & KROGH, K. 2012. Gastrointestinal transit times and motility in patients with cystic fibrosis. *Scand J Gastroenterol,* 47**,** 920-6.
- HOJO, M., ASAHARA, T., NAGAHARA, A., TAKEDA, T., MATSUMOTO, K., UEYAMA, H., MATSUMOTO, K., ASAOKA, D., TAKAHASHI, T., NOMOTO, K., YAMASHIRO, Y. & WATANABE, S. 2018. Gut Microbiota Composition Before and After Use of Proton Pump Inhibitors. *Dig Dis Sci,* 63**,** 2940-2949.
- HUYCKE, M. M., ABRAMS, V. & MOORE, D. R. 2002. Enterococcus faecalis produces extracellular superoxide and hydrogen peroxide that damages colonic epithelial cell DNA. *Carcinogenesis,* 23**,** 529-536.
- IMHANN, F., BONDER, M. J., VICH VILA, A., FU, J., MUJAGIC, Z., VORK, L., TIGCHELAAR, E. F., JANKIPERSADSING, S. A., CENIT, M. C., HARMSEN, H. J. M., DIJKSTRA, G., FRANKE, L., XAVIER, R. J., JONKERS, D., WIJMENGA, C., WEERSMA, R. K. & ZHERNAKOVA, A. 2016. Proton pump inhibitors affect the gut microbiome. *Gut,* 65**,** 740.
- JAUDSZUS, A., PFEIFER, E., LORENZ, M., BEIERSDORF, N., HIPLER, U. C., ZAGOYA, C. & MAINZ, J. G. 2022. Abdominal Symptoms Assessed With the CFAbd-Score are Associated With Intestinal Inflammation in Patients With Cystic Fibrosis. *J Pediatr Gastroenterol Nutr,* 74**,** 355-360.
- JAKOBSSON, H. E., JERNBERG, C., ANDERSSON, A. F., SJÖLUND-KARLSSON, M., JANSSON, J. K. & ENGSTRAND, L. 2010. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. *PLoS One,* 5**,** e9836.
- JAROSZ-GRIFFITHS, H. H., SCAMBLER, T., WONG, C. H., LARA-REYNA, S., HOLBROOK, J., MARTINON, F., SAVIC, S., WHITAKER, P., ETHERINGTON, C., SPOLETINI, G., CLIFTON, I., MEHTA, A., MCDERMOTT, M. F. & PECKHAM, D. 2020. Different CFTR modulator combinations downregulate inflammation differently in cystic fibrosis. *Elife,* 9.
- JIANG, W., WU, N., WANG, X., CHI, Y., ZHANG, Y., QIU, X., HU, Y., LI, J. & LIU, Y. 2015. Dysbiosis gut microbiota associated with inflammation and impaired mucosal immune function in intestine of humans with non-alcoholic fatty liver disease. *Sci Rep,* 5**,** 8096.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- KAETZEL, C. S. 2014. Cooperativity among secretory IgA, the polymeric immunoglobulin receptor, and the gut microbiota promotes host-microbial mutualism. *Immunol Lett,* 162**,** 10-21.
- KANG, C., WANG, B., KALIANNAN, K., WANG, X., LANG, H., HUI, S., HUANG, L., ZHANG, Y., ZHOU, M., CHEN, M. & MI, M. 2017. Gut Microbiota Mediates the Protective Effects of Dietary Capsaicin against Chronic Low-Grade Inflammation and Associated Obesity Induced by High-Fat Diet. *mBio,* 8.
- KASHTANOVA, D. A., TKACHEVA, O. N., DOUDINSKAYA, E. N., STRAZHESKO, I. D., KOTOVSKAYA, Y. V., POPENKO, A. S., TYAKHT, A. V. & ALEXEEV, D. G. 2018. Gut Microbiota in Patients with Different Metabolic Statuses: Moscow Study. *Microorganisms,* 6.
- KELLY, C. J., ZHENG, L., CAMPBELL, E. L., SAEEDI, B., SCHOLZ, C. C., BAYLESS, A. J., WILSON, K. E., GLOVER, L. E., KOMINSKY, D. J., MAGNUSON, A., WEIR, T. L., EHRENTRAUT, S. F., PICKEL, C., KUHN, K. A., LANIS, J. M., NGUYEN, V., TAYLOR, C. T. & COLGAN, S. P. 2015. Crosstalk between Microbiota-Derived Short-Chain Fatty Acids and Intestinal Epithelial HIF Augments Tissue Barrier Function. *Cell Host Microbe,* 17**,** 662-71.
- KHOKHLOVA, E. V., SMEIANOV, V. V., EFIMOV, B. A., KAFARSKAIA, L. I., PAVLOVA, S. I. & SHKOPOROV, A. N. 2012. Anti-inflammatory properties of intestinal Bifidobacterium strains isolated from healthy infants. *Microbiol Immunol,* 56**,** 27-39.
- KIM, Y. G., UDAYANGA, K. G., TOTSUKA, N., WEINBERG, J. B., NÚÑEZ, G. & SHIBUYA, A. 2014. Gut dysbiosis promotes M2 macrophage polarization and allergic airway inflammation via fungi-induced PGE_2. *Cell Host Microbe,* 15**,** 95-102.
- KORPELA, K., SALONEN, A., VIRTA, L. J., KEKKONEN, R. A., FORSLUND, K., BORK, P. & DE VOS, W. M. 2016. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nat Commun,* 7**,** 10410.
- KRISTENSEN, M., PREVAES, S., KALKMAN, G., TRAMPER-STRANDERS, G. A., HASRAT, R., DE WINTER-DE GROOT, K. M., JANSSENS, H. M., TIDDENS, H. A., VAN WESTREENEN, M., SANDERS, E. A. M., ARETS, B., KEIJSER, B., VAN DER ENT, C. K. & BOGAERT, D. 2020. Development of the gut microbiota in early life: The impact of cystic fibrosis and antibiotic treatment. *J Cyst Fibros,* 19**,** 553-561.
- KUMAR SINGH, A., CABRAL, C., KUMAR, R., GANGULY, R., KUMAR RANA, H., GUPTA, A., ROSARIA LAURO, M., CARBONE, C., REIS, F. & PANDEY, A. K. 2019. Beneficial Effects of Dietary Polyphenols on Gut Microbiota and Strategies to Improve Delivery Efficiency. *Nutrients,* 11.
- LAHEIJ, R. J., STURKENBOOM, M. C., HASSING, R. J., DIELEMAN, J., STRICKER, B. H. & JANSEN, J. B. 2004. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *Jama,* 292**,** 1955-60.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- LANGDON, A., CROOK, N. & DANTAS, G. 2016. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Med,* 8**,** 39.
- LARROSA, M., YAÑÉZ-GASCÓN, M. J., SELMA, M. V., GONZÁLEZ-SARRÍAS, A., TOTI, S., CERÓN, J. J., TOMÁS-BARBERÁN, F., DOLARA, P. & ESPÍN, J. C. 2009. Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model. *J Agric Food Chem,* 57**,** 2211-20.
- LE CHATELIER, E., NIELSEN, T., QIN, J., PRIFTI, E., HILDEBRAND, F., FALONY, G., ALMEIDA, M., ARUMUGAM, M., BATTO, J. M., KENNEDY, S., LEONARD, P., LI, J., BURGDORF, K., GRARUP, N., JØRGENSEN, T., BRANDSLUND, I., NIELSEN, H. B., JUNCKER, A. S., BERTALAN, M., LEVENEZ, F., PONS, N., RASMUSSEN, S., SUNAGAWA, S., TAP, J., TIMS, S., ZOETENDAL, E. G., BRUNAK, S., CLÉMENT, K., DORÉ, J., KLEEREBEZEM, M., KRISTIANSEN, K., RENAULT, P., SICHERITZ-PONTEN, T., DE VOS, W. M., ZUCKER, J. D., RAES, J., HANSEN, T., BORK, P., WANG, J., EHRLICH, S. D. & PEDERSEN, O. 2013. Richness of human gut microbiome correlates with metabolic markers. *Nature,* 500**,** 541-6.
- LEE, S. H., YUN, Y., KIM, S. J., LEE, E. J., CHANG, Y., RYU, S., SHIN, H., KIM, H. L., KIM, H. N. & LEE, J. H. 2018. Association between Cigarette Smoking Status and Composition of Gut Microbiota: Population-Based Cross-Sectional Study. *J Clin Med,* 7.
- LEHMANN, S., HILLER, J., VAN BERGENHENEGOUWEN, J., KNIPPELS, L. M., GARSSEN, J. & TRAIDL-HOFFMANN, C. 2015. In Vitro Evidence for Immune-Modulatory Properties of Non-Digestible Oligosaccharides: Direct Effect on Human Monocyte Derived Dendritic Cells. *PLoS One,* 10**,** e0132304.
- LI, L. & SOMERSET, S. 2014. Digestive system dysfunction in cystic fibrosis: challenges for nutrition therapy. *Dig Liver Dis,* 46**,** 865-74.
- LING, X., LINGLONG, P., WEIXIA, D. & HONG, W. 2016. Protective Effects of Bifidobacterium on Intestinal Barrier Function in LPS-Induced Enterocyte Barrier Injury of Caco-2 Monolayers and in a Rat NEC Model. *PLoS One,* 11**,** e0161635.
- LIU, F., LI, J., GUAN, Y., LOU, Y., CHEN, H., XU, M., DENG, D., CHEN, J., NI, B., ZHAO, L., LI, H., SANG, H. & CAI, X. 2019. Dysbiosis of the Gut Microbiome is associated with Tumor Biomarkers in Lung Cancer. *International journal of biological sciences,* 15**,** 2381-2392.
- LLEWELLYN, S. R., BRITTON, G. J., CONTIJOCH, E. J., VENNARO, O. H., MORTHA, A., COLOMBEL, J. F., GRINSPAN, A., CLEMENTE, J. C., MERAD, M. & FAITH, J. J. 2018. Interactions Between Diet and the Intestinal Microbiota Alter Intestinal Permeability and Colitis Severity in Mice. *Gastroenterology,* 154**,** 1037-1046.e2.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- LOPETUSO, L. R., SCALDAFERRI, F., PETITO, V. & GASBARRINI, A. 2013. Commensal Clostridia: leading players in the maintenance of gut homeostasis. *Gut Pathog,* 5**,** 23.
- MAISONNEUVE, P., FITZSIMMONS, S. C., NEGLIA, J. P., CAMPBELL, P. W., 3RD & LOWENFELS, A. B. 2003. Cancer risk in nontransplanted and transplanted cystic fibrosis patients: a 10-year study. *J Natl Cancer Inst,* 95**,** 381-7.
- MAISONNEUVE, P., MARSHALL, B. C., KNAPP, E. A. & LOWENFELS, A. B. 2013. Cancer risk in cystic fibrosis: a 20-year nationwide study from the United States. *J Natl Cancer Inst,* 105**,** 122-9.
- MAINZ, J. G., ZAGOYA, C., POLTE, L., NAEHRLICH, L., SASSE, L., EICKMEIER, O., SMACZNY, C., BARUCHA, A., BECHINGER, L., DUCKSTEIN, F., KURZIDIM, L., ESCHENHAGEN, P., CALEY, L., PECKHAM, D. & SCHWARZ, C. 2022. Elexacaftor-Tezacaftor-Ivacaftor Treatment Reduces Abdominal Symptoms in Cystic Fibrosis-Early results Obtained With the CF-Specific CFAbd-Score. *Front Pharmacol,* 13**,** 877118.
- MATERA, G., MUTO, V., VINCI, M., ZICCA, E., ABDOLLAHI-ROODSAZ, S., VAN DE VEERDONK, F. L., KULLBERG, B. J., LIBERTO, M. C., VAN DER MEER, J. W., FOCÀ, A., NETEA, M. G. & JOOSTEN, L. A. 2009. Receptor recognition of and immune intracellular pathways for Veillonella parvula lipopolysaccharide. *Clin Vaccine Immunol,* 16**,** 1804-9.
- MATSUOKA, K. & KANAI, T. 2015. The gut microbiota and inflammatory bowel disease. *Semin Immunopathol,* 37**,** 47-55.
- MCKENZIE, C., TAN, J., MACIA, L. & MACKAY, C. R. 2017. The nutrition-gut microbiome-physiology axis and allergic diseases. *Immunol Rev,* 278**,** 277-295.
- MCRORIE, J. W., JR. 2015a. Evidence-Based Approach to Fiber Supplements and Clinically Meaningful Health Benefits, Part 1: What to Look for and How to Recommend an Effective Fiber Therapy. *Nutr Today,* 50**,** 82-89.
- MCRORIE, J. W., JR. 2015b. Evidence-Based Approach to Fiber Supplements and Clinically Meaningful Health Benefits, Part 2: What to Look for and How to Recommend an Effective Fiber Therapy. *Nutr Today,* 50**,** 90-97.
- MERKEL, P. A. 1999. Rheumatic disease and cystic fibrosis. *Arthritis Rheum,* 42**,** 1563-71.
- MOLINA, M. A., DÍAZ, A. M., HESSE, C., GINTER, W., GENTILINI, M. V., NUÑEZ, G. G., CANELLADA, A. M., SPARWASSER, T., BEROD, L., CASTRO, M. S. & MANGHI, M. A. 2015. Immunostimulatory Effects Triggered by Enterococcus faecalis CECT7121 Probiotic Strain Involve Activation of Dendritic Cells and Interferon-Gamma Production. *PloS one,* 10**,** e0127262-e0127262.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- MONDA, V., VILLANO, I., MESSINA, A., VALENZANO, A., ESPOSITO, T., MOSCATELLI, F., VIGGIANO, A., CIBELLI, G., CHIEFFI, S., MONDA, M. & MESSINA, G. 2017. Exercise Modifies the Gut Microbiota with Positive Health Effects. *Oxidative medicine and cellular longevity,* 2017**,** 3831972-3831972.
- MUKHERJEE, A., LORDAN, C., ROSS, R. P. & COTTER, P. D. 2020. Gut microbes from the phylogenetically diverse genus Eubacterium and their various contributions to gut health. *Gut microbes,* 12**,** 1802866-1802866.
- NABIZADEH, E., JAZANI, N. H., BAGHERI, M. & SHAHABI, S. 2017. Association of altered gut microbiota composition with chronic urticaria. *Ann Allergy Asthma Immunol,* 119**,** 48-53.
- NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. 2014. *Faecal microbiota transplant for recurrent Clostridium difficile infection* [Online]. Available: https://www.nice.org.uk/guidance/ipg485/resources/faecal-microbiota-transplant-for-recurrent-clostridium-difficile-infection-pdf-1899869993554885 [Accessed 1st January 2021].
- NIELSEN, S., NEEDHAM, B., LEACH, S. T., DAY, A. S., JAFFE, A., THOMAS, T. & OOI, C. Y. 2016. Disrupted progression of the intestinal microbiota with age in children with cystic fibrosis. *Scientific reports,* 6**,** 24857.
- O'CALLAGHAN, A. & VAN SINDEREN, D. 2016. Bifidobacteria and Their Role as Members of the Human Gut Microbiota. *Frontiers in microbiology,* 7**,** 925-925.
- OKUDA, J., HAYASHI, N., OKAMOTO, M., SAWADA, S., MINAGAWA, S., YANO, Y. & GOTOH, N. 2010. Translocation of Pseudomonas aeruginosa from the intestinal tract is mediated by the binding of ExoS to an Na,K-ATPase regulator, FXYD3. *Infection and immunity,* 78**,** 4511-4522.
- OOI, C. Y., SYED, S. A., ROSSI, L., GARG, M., NEEDHAM, B., AVOLIO, J., YOUNG, K., SURETTE, M. G. & GONSKA, T. 2018. Impact of CFTR modulation with Ivacaftor on Gut Microbiota and Intestinal Inflammation. *Sci Rep,* 8**,** 17834.
- OTTMAN, N., REUNANEN, J., MEIJERINK, M., PIETILÄ, T. E., KAINULAINEN, V., KLIEVINK, J., HUUSKONEN, L., AALVINK, S., SKURNIK, M., BOEREN, S., SATOKARI, R., MERCENIER, A., PALVA, A., SMIDT, H., DE VOS, W. M. & BELZER, C. 2017. Pili-like proteins of Akkermansia muciniphila modulate host immune responses and gut barrier function. *PLoS One,* 12**,** e0173004.
- PENDERS, J., VINK, C., DRIESSEN, C., LONDON, N., THIJS, C. & STOBBERINGH, E. E. 2005. Quantification of Bifidobacterium spp., Escherichia coli and Clostridium difficile in faecal samples of breast-fed and formula-fed infants by real-time PCR. *FEMS Microbiol Lett,* 243**,** 141-7.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- PENG, L., LI, Z.-R., GREEN, R. S., HOLZMAN, I. R. & LIN, J. 2009. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *The Journal of nutrition,* 139**,** 1619-1625.
- PLÖGER, S., STUMPFF, F., PENNER, G. B., SCHULZKE, J. D., GÄBEL, G., MARTENS, H., SHEN, Z., GÜNZEL, D. & ASCHENBACH, J. R. 2012. Microbial butyrate and its role for barrier function in the gastrointestinal tract. *Ann N Y Acad Sci,* 1258**,** 52-9.
- PUSTELNY, C., KOMOR, U., PAWAR, V., LORENZ, A., BIELECKA, A., MOTER, A., GOCHT, B., ECKWEILER, D., MÜSKEN, M., GROTHE, C., LÜNSDORF, H., WEISS, S. & HÄUSSLER, S. 2015. Contribution of Veillonella parvula to Pseudomonas aeruginosa-mediated pathogenicity in a murine tumor model system. *Infect Immun,* 83**,** 417-29.
- RANDAZZO, A., KORNREICH, A. & LISSOIR, B. 2015. A Clostridium hathewayi isolate in blood culture of a patient with an acute appendicitis. *Anaerobe,* 35**,** 44-7.
- RAYMOND, F., OUAMEUR, A. A., DÉRASPE, M., IQBAL, N., GINGRAS, H., DRIDI, B., LEPROHON, P., PLANTE, P. L., GIROUX, R., BÉRUBÉ, È., FRENETTE, J., BOUDREAU, D. K., SIMARD, J. L., CHABOT, I., DOMINGO, M. C., TROTTIER, S., BOISSINOT, M., HULETSKY, A., ROY, P. H., OUELLETTE, M., BERGERON, M. G. & CORBEIL, J. 2016. The initial state of the human gut microbiome determines its reshaping by antibiotics. *Isme j,* 10**,** 707-20.
- ROCHA-RAMÍREZ, L. M., PÉREZ-SOLANO, R. A., CASTAÑÓN-ALONSO, S. L., MORENO GUERRERO, S. S., RAMÍREZ PACHECO, A., GARCÍA GARIBAY, M. & ESLAVA, C. 2017. Probiotic Lactobacillus Strains Stimulate the Inflammatory Response and Activate Human Macrophages. *J Immunol Res,* 2017**,** 4607491.
- RONAN, N. J., EINARSSON, G. G., DEANE, J., FOUHY, F., REA, M., HILL, C., SHANAHAN, F., ELBORN, J. S., ROSS, R. P., MCCARTHY, M., MURPHY, D. M., EUSTACE, J. A., MM, T., STANTON, C. & PLANT, B. J. 2022. Modulation, microbiota and inflammation in the adult CF gut: A prospective study. *J Cyst Fibros,* 21**,** 837-843.
- SALEM, F., KINDT, N., MARCHESI, J. R., NETTER, P., LOPEZ, A., KOKTEN, T., DANESE, S., JOUZEAU, J. Y., PEYRIN-BIROULET, L. & MOULIN, D. 2019. Gut microbiome in chronic rheumatic and inflammatory bowel diseases: Similarities and differences. *United European Gastroenterol J,* 7**,** 1008-1032.
- SANSONETTI, P. J., PHALIPON, A., ARONDEL, J., THIRUMALAI, K., BANERJEE, S., AKIRA, S., TAKEDA, K. & ZYCHLINSKY, A. 2000. Caspase-1 Activation of IL-1β and IL-18 Are Essential for Shigella flexneri–Induced Inflammation. *Immunity,* 12**,** 581-590.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- SCAMBLER, T., JAROSZ-GRIFFITHS, H. H., LARA-REYNA, S., PATHAK, S., WONG, C., HOLBROOK, J., MARTINON, F., SAVIC, S., PECKHAM, D. & MCDERMOTT, M. F. 2019. ENaC-mediated sodium influx exacerbates NLRP3-dependent inflammation in cystic fibrosis. *Elife,* 8.
- SCHWARZENBERG, S. J., VU, P. T., SKALLAND, M., HOFFMAN, L. R., POPE, C., GELFOND, D., NARKEWICZ, M. R., NICHOLS, D. P., HELTSHE, S. L., DONALDSON, S. H., FREDERICK, C. A., KELLY, A., PITTMAN, J. E., RATJEN, F., ROSENFELD, M., SAGEL, S. D., SOLOMON, G. M., STALVEY, M. S., CLANCY, J. P., ROWE, S. M. & FREEDMAN, S. D. 2022. Elexacaftor/tezacaftor/ivacaftor and gastrointestinal outcomes in cystic fibrosis: Report of promise-GI. *J Cyst Fibros*.
- SCHER, J. U., UBEDA, C., ARTACHO, A., ATTUR, M., ISAAC, S., REDDY, S. M., MARMON, S., NEIMANN, A., BRUSCA, S., PATEL, T., MANASSON, J., PAMER, E. G., LITTMAN, D. R. & ABRAMSON, S. B. 2015. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. *Arthritis Rheumatol,* 67**,** 128-39.
- SCHIRMER, M., SMEEKENS, S. P., VLAMAKIS, H., JAEGER, M., OOSTING, M., FRANZOSA, E. A., TER HORST, R., JANSEN, T., JACOBS, L., BONDER, M. J., KURILSHIKOV, A., FU, J., JOOSTEN, L. A. B., ZHERNAKOVA, A., HUTTENHOWER, C., WIJMENGA, C., NETEA, M. G. & XAVIER, R. J. 2016. Linking the Human Gut Microbiome to Inflammatory Cytokine Production Capacity. *Cell,* 167**,** 1125-1136.e8.
- SCHROEDER, B. O., BIRCHENOUGH, G. M. H., STÅHLMAN, M., ARIKE, L., JOHANSSON, M. E. V., HANSSON, G. C. & BÄCKHED, F. 2018. Bifidobacteria or Fiber Protects against Diet-Induced Microbiota-Mediated Colonic Mucus Deterioration. *Cell Host Microbe,* 23**,** 27-40.e7.
- SCHULTHESS, J., PANDEY, S., CAPITANI, M., RUE-ALBRECHT, K. C., ARNOLD, I., FRANCHINI, F., CHOMKA, A., ILOTT, N. E., JOHNSTON, D. G. W., PIRES, E., MCCULLAGH, J., SANSOM, S. N., ARANCIBIA-CARCAMO, C. V., UHLIG, H. H. & POWRIE, F. 2019. The Short Chain Fatty Acid Butyrate Imprints an Antimicrobial Program in Macrophages. *Immunity,* 50**,** 432-445.e7.
- SEISHIMA, J., IIDA, N., KITAMURA, K., YUTANI, M., WANG, Z., SEKI, A., YAMASHITA, T., SAKAI, Y., HONDA, M., YAMASHITA, T., KAGAYA, T., SHIROTA, Y., FUJINAGA, Y., MIZUKOSHI, E. & KANEKO, S. 2019. Gut-derived Enterococcus faecium from ulcerative colitis patients promotes colitis in a genetically susceptible mouse host. *Genome Biol,* 20**,** 252.
- SENDER, R., FUCHS, S. & MILO, R. 2016. Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans. *Cell,* 164**,** 337-40.
- SINGH, L., CARIAPPA, M. P. & KAUR, M. 2016. Klebsiella oxytoca: An emerging pathogen? *Medical journal, Armed Forces India,* 72**,** S59-S61.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- SMYTH, R. L., CROFT, N. M., O'HEA, U., MARSHALL, T. G. & FERGUSON, A. 2000. Intestinal inflammation in cystic fibrosis. *Arch Dis Child,* 82**,** 394-9.
- SOKOL, H., PIGNEUR, B., WATTERLOT, L., LAKHDARI, O., BERMÚDEZ-HUMARÁN, L. G., GRATADOUX, J. J., BLUGEON, S., BRIDONNEAU, C., FURET, J. P., CORTHIER, G., GRANGETTE, C., VASQUEZ, N., POCHART, P., TRUGNAN, G., THOMAS, G., BLOTTIÈRE, H. M., DORÉ, J., MARTEAU, P., SEKSIK, P. & LANGELLA, P. 2008. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci U S A,* 105**,** 16731-6.
- STALLINGS, V. A., SAINATH, N., OBERLE, M., BERTOLASO, C. & SCHALL, J. I. 2018. Energy Balance and Mechanisms of Weight Gain with Ivacaftor Treatment of Cystic Fibrosis Gating Mutations. *J Pediatr,* 201**,** 229-237.e4.
- STANISLAWSKI, M. A., DABELEA, D., WAGNER, B. D., ISZATT, N., DAHL, C., SONTAG, M. K., KNIGHT, R., LOZUPONE, C. A. & EGGESBØ, M. 2018. Gut Microbiota in the First 2 Years of Life and the Association with Body Mass Index at Age 12 in a Norwegian Birth Cohort. *mBio,* 9.
- STEWART, C. J., AJAMI, N. J., O'BRIEN, J. L., HUTCHINSON, D. S., SMITH, D. P., WONG, M. C., ROSS, M. C., LLOYD, R. E., DODDAPANENI, H., METCALF, G. A., MUZNY, D., GIBBS, R. A., VATANEN, T., HUTTENHOWER, C., XAVIER, R. J., REWERS, M., HAGOPIAN, W., TOPPARI, J., ZIEGLER, A. G., SHE, J. X., AKOLKAR, B., LERNMARK, A., HYOTY, H., VEHIK, K., KRISCHER, J. P. & PETROSINO, J. F. 2018. Temporal development of the gut microbiome in early childhood from the TEDDY study. *Nature,* 562**,** 583-588.
- SZENTPETERY, S., FERNANDEZ, G. S., SCHECHTER, M. S., JAIN, R., FLUME, P. A. & FINK, A. K. 2022. Obesity in Cystic fibrosis: prevalence, trends and associated factors data from the US cystic fibrosis foundation patient registry. *J Cyst Fibros*.
- TÉTARD, C., MITTAINE, M., BUI, S., BEAUFILS, F., MAUMUS, P., FAYON, M., BURGEL, P. R., LAMIREAU, T., DELHAES, L., MAS, E. & ENAUD, R. 2020. Reduced Intestinal Inflammation With Lumacaftor/Ivacaftor in Adolescents With Cystic Fibrosis. *J Pediatr Gastroenterol Nutr,* 71**,** 778-781.
- THERIOT, C. M., KOENIGSKNECHT, M. J., CARLSON, P. E., HATTON, G. E., NELSON, A. M., LI, B., HUFFNAGLE, G. B., Z. LI, J. & YOUNG, V. B. 2014. Antibiotic-induced shifts in the mouse gut microbiome and metabolome increase susceptibility to Clostridium difficile infection. *Nature Communications,* 5**,** 3114.
- TIDJANI ALOU, M., MILLION, M., TRAORE, S. I., MOUELHI, D., KHELAIFIA, S., BACHAR, D., CAPUTO, A., DELERCE, J., BRAH, S., ALHOUSSEINI, D., SOKHNA, C., ROBERT, C., DIALLO, B. A., DIALLO, A., PAROLA, P., GOLDEN, M., LAGIER, J. C. & RAOULT, D. 2017. Gut Bacteria Missing in Severe Acute Malnutrition, Can We Identify Potential Probiotics by Culturomics? *Front Microbiol,* 8**,** 899.
- TOPRAK, N. U., ÖZCAN, E. T., PEKIN, T., YUMUK, P. F. & SOYLETIR, G. 2014. Bacteraemia caused by Clostridium symbiosum: case report and review of the literature. *Indian J Med Microbiol,* 32**,** 92-4.
- TROMPETTE, A., GOLLWITZER, E. S., PATTARONI, C., LOPEZ-MEJIA, I. C., RIVA, E., PERNOT, J., UBAGS, N., FAJAS, L., NICOD, L. P. & MARSLAND, B. J. 2018. Dietary Fiber Confers Protection against Flu by Shaping Ly6c(-) Patrolling Monocyte Hematopoiesis and CD8(+) T Cell Metabolism. *Immunity,* 48**,** 992-1005 e8.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- TUOVINEN, E., KETO, J., NIKKILÄ, J., MÄTTÖ, J. & LÄHTEENMÄKI, K. 2013. Cytokine response of human mononuclear cells induced by intestinal Clostridium species. *Anaerobe,* 19**,** 70-76.
- VAN DEN ELSEN, L. W. J., GARSSEN, J., BURCELIN, R. & VERHASSELT, V. 2019. Shaping the Gut Microbiota by Breastfeeding: The Gateway to Allergy Prevention? *Frontiers in pediatrics,* 7**,** 47-47.
- VATANEN, T., KOSTIC, A. D., D'HENNEZEL, E., SILJANDER, H., FRANZOSA, E. A., YASSOUR, M., KOLDE, R., VLAMAKIS, H., ARTHUR, T. D., HÄMÄLÄINEN, A. M., PEET, A., TILLMANN, V., UIBO, R., MOKUROV, S., DORSHAKOVA, N., ILONEN, J., VIRTANEN, S. M., SZABO, S. J., PORTER, J. A., LÄHDESMÄKI, H., HUTTENHOWER, C., GEVERS, D., CULLEN, T. W., KNIP, M., XAVIER, R. J. & GROUP, D. S. 2016. Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans. *Cell,* 165**,** 1551.
- VERNOCCHI, P., DEL CHIERICO, F., RUSSO, A., MAJO, F., ROSSITTO, M., VALERIO, M., CASADEI, L., LA STORIA, A., DE FILIPPIS, F., RIZZO, C., MANETTI, C., PACI, P., ERCOLINI, D., MARINI, F., FISCARELLI, E. V., DALLAPICCOLA, B., LUCIDI, V., MICCHELI, A. & PUTIGNANI, L. 2018. Gut microbiota signatures in cystic fibrosis: Loss of host CFTR function drives the microbiota enterophenotype. *PLoS One,* 13**,** e0208171.
- VIRTA, L., AUVINEN, A., HELENIUS, H., HUOVINEN, P. & KOLHO, K. L. 2012. Association of repeated exposure to antibiotics with the development of pediatric Crohn's disease--a nationwide, register-based finnish case-control study. *Am J Epidemiol,* 175**,** 775-84.
- WAN, Y., YUAN, J., LI, J., LI, H., YIN, K., WANG, F. & LI, D. 2020. Overweight and underweight status are linked to specific gut microbiota and intestinal tricarboxylic acid cycle intermediates. *Clin Nutr,* 39**,** 3189-3198.
- WANG, S., HIBBERD, M. L., PETTERSSON, S. & LEE, Y. K. 2014. Enterococcus faecalis from healthy infants modulates inflammation through MAPK signaling pathways. *PloS one,* 9**,** e97523-e97523.
- WANG, T., CAI, G., QIU, Y., FEI, N., ZHANG, M., PANG, X., JIA, W., CAI, S. & ZHAO, L. 2012. Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. *Isme j,* 6**,** 320-9.
- WANG, Y., LEONG, L. E. X., KEATING, R. L., KANNO, T., ABELL, G. C. J., MOBEGI, F. M., CHOO, J. M., WESSELINGH, S. L., MASON, A. J., BURR, L. D. & ROGERS, G. B. 2018. Opportunistic bacteria confer the ability to ferment prebiotic starch in the adult cystic fibrosis gut. *Gut Microbes.*

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- WEI, Z., CAO, S., LIU, S., YAO, Z., SUN, T., LI, Y., LI, J., ZHANG, D. & ZHOU, Y. 2016. Could gut microbiota serve as prognostic biomarker associated with colorectal cancer patients' survival? A pilot study on relevant mechanism. *Oncotarget,* 7**,** 46158-46172.
- WEXLER, H. M. 2007. Bacteroides: the good, the bad, and the nitty-gritty. *Clinical microbiology reviews,* 20**,** 593-621.
- WLODARSKA, M., WILLING, B., KEENEY, K. M., MENENDEZ, A., BERGSTROM, K. S., GILL, N., RUSSELL, S. L., VALLANCE, B. A. & FINLAY, B. B. 2011. Antibiotic treatment alters the colonic mucus layer and predisposes the host to exacerbated Citrobacter rodentium-induced colitis. *Infect Immun,* 79**,** 1536-45.
- YAMADA, A., KOMAKI, Y., KOMAKI, F., MICIC, D., ZULLOW, S. & SAKURABA, A. 2018. Risk of gastrointestinal cancers in patients with cystic fibrosis: a systematic review and meta-analysis. *Lancet Oncol,* 19**,** 758-767.
- YANG, Y. & JOBIN, C. 2014. Microbial imbalance and intestinal pathologies: connections and contributions. *Disease models & mechanisms,* 7**,** 1131-1142.
- YOSHIDA, N., EMOTO, T., YAMASHITA, T., WATANABE, H., HAYASHI, T., TABATA, T., HOSHI, N., HATANO, N., OZAWA, G., SASAKI, N., MIZOGUCHI, T., AMIN, H. Z., HIROTA, Y., OGAWA, W., YAMADA, T. & HIRATA, K.-I. 2018. Bacteroides vulgatus and Bacteroides dorei Reduce Gut Microbial Lipopolysaccharide Production and Inhibit Atherosclerosis. *Circulation,* 138**,** 2486-2498.
- YOUNG, C., WOOD, H. M., FUENTES BALAGUER, A., BOTTOMLEY, D., GALLOP, N., WILKINSON, L., BENTON, S. C., BREALEY, M., JOHN, C., BURTONWOOD, C., THOMPSON, K. N., YAN, Y., BARRETT, J. H., MORRIS, E. J. A., HUTTENHOWER, C. & QUIRKE, P. 2021a. Microbiome Analysis of More Than 2,000 NHS Bowel Cancer Screening Programme Samples Shows the Potential to Improve Screening Accuracy. *Clin Cancer Res,* 27**,** 2246-2254.
- YOUNG, C., WOOD, H. M., SESHADRI, R. A., VAN NANG, P., VACCARO, C., MELENDEZ, L. C., BOSE, M., VAN DOI, M., PIÑERO, T. A., VALLADARES, C. T., ARGUERO, J., BALAGUER, A. F., THOMPSON, K. N., YAN, Y., HUTTENHOWER, C. & QUIRKE, P. 2021b. The colorectal cancer-associated faecal microbiome of developing countries resembles that of developed countries. *Genome Med,* 13**,** 27.
- ZABORINA, O., KOHLER, J. E., WANG, Y., BETHEL, C., SHEVCHENKO, O., WU, L., TURNER, J. R. & ALVERDY, J. C. 2006. Identification of multi-drug resistant Pseudomonas aeruginosa clinical isolates that are highly disruptive to the intestinal epithelial barrier. *Annals of clinical microbiology and antimicrobials,* 5**,** 14-14.
- ZHANG, W. Q., ZHAO, S. K., LUO, J. W., DONG, X. P., HAO, Y. T., LI, H., SHAN, L., ZHOU, Y., SHI, H. B., ZHANG, Z. Y., PENG, C. L. & ZHAO, X. G. 2018. Alterations of fecal bacterial communities in patients with lung cancer. *Am J Transl Res,* 10**,** 3171-3185.
- ZHANG, D., LI, S., WANG, N., TAN, H. Y., ZHANG, Z. & FENG, Y. 2020a. The Cross-Talk Between Gut Microbiota and Lungs in Common Lung Diseases. *Front Microbiol,* 11**,** 301.

Cystic Fibrosis Trust

References

UNIVERSITY OF LEEDS

- ZHANG, Y., HOU, Q., MA, C., ZHAO, J., XU, H., LI, W., WANG, Y., MA, H., ZHANG, H. & SUN, Z. 2020. Lactobacillus casei protects dextran sodium sulfate- or rapamycin-induced colonic inflammation in the mouse. *Eur J Nutr,* 59**,** 1443-1451.
- ZHAO, S., LIU, W., WANG, J., SHI, J., SUN, Y., WANG, W., NING, G., LIU, R. & HONG, J. 2017. Akkermansia muciniphila improves metabolic profiles by reducing inflammation in chow diet-fed mice. *J Mol Endocrinol,* 58**,** 1-14.
- ZHENG, H., LIANG, H., WANG, Y., MIAO, M., SHI, T., YANG, F., LIU, E., YUAN, W., JI, Z. S. & LI, D. K. 2016. Altered Gut Microbiota Composition Associated with Eczema in Infants. *PLoS One,* 11**,** e0166026.
- ZHU, C., SONG, K., SHEN, Z., QUAN, Y., TAN, B., LUO, W., WU, S., TANG, K., YANG, Z. & WANG, X. 2018. Roseburia intestinalis inhibits interleukin-17 excretion and promotes regulatory T cells differentiation in colitis. *Molecular medicine reports,* 17**,** 7567-7574.

Cystic Fibrosis Trust