Economic Potential of Probiotic Supplementation in Institutionalized Elderly with Chronic Constipation

J. Flach, M. Koks, M.B. van der Waal, E. Claassen, O.F.A. Larsen

5.1 ABSTRACT

Probiotics have been suggested as an effective supplementation to conventional treatment regimens for chronic constipation in nursing homes, but the financial impact of the intervention for these institutions remains to be determined. We therefore set out to investigate the economic potential of probiotic supplementation in a nursing home setting with regard to constipation management. We aimed to determine the probiotic lower efficacy limit required to reduce the institution’s constipation-related expenses, based on quantitative data obtained from nursing home employees. A meta-analysis was conducted on clinical studies reporting the effects of probiotic intervention on constipation status in institutionalized elderly, in order to estimate the probiotic treatment effect. Our results indicate that the constipation-related expenses of an average-sized nursing home with 100 residents and a constipation prevalence of 42%, amount to approximately €90,000 per year. Daily probiotic supplementation of all nursing home residents may reduce the institution’s expenses by €8,000-€25,000 annually, as probiotic intervention is suggested to lower the constipation prevalence by 28%. To further substantiate the proposed economic potential of probiotic supplementation, however, it is recommended that the probiotic treatment effect on the workload for nursing home employees is addressed in appropriately scaled and controlled future clinical trials.

**Keywords:** Probiotics; Constipation; Elderly; Nursing Homes; Meta-analysis; Health Economics.
5.2 INTRODUCTION

The world population is aging at an unprecedented rate according to the World Health Organization (WHO, 2011). It is projected that the global population of elderly will more than double over the course of half a century (WHO, 2011). The aging population poses new challenges on health care management, as aging is a risk factor for disease and associated with increased frailty (Karunanathan et al., 2009; Fried & Ferrucci, 2016). Health care expenditures are therefore expected to rise (WHO, 2011) with an increasing burden on the global economy. One of the leading chronic diseases amongst elderly is constipation (Gallegos-Orozco et al., 2012). Changes in the composition and diversity of the microbiota, associated with aging and polypharmacy (Odamaki et al., 2016; Ticinesi et al., 2017), make elderly citizens highly vulnerable to gastrointestinal disease. Institutionalized elderly are especially at risk due to a lack of exercise and poor dietary standards, common to these institutions (Cereda et al., 2016; De Souto Barreto et al., 2015). We showed that a poignant average of ~62% of elderly nursing home residents is constipated (Larsen et al., 2017). Chronic constipation has a detrimental influence on health-related quality of life (Bongers et al., 2009; Wang et al., 2008; Norton, 2006; Hjaltadóttir & Gústafsdóttir, 2007) and drains a substantial portion of the institutions’ budget in treatment and care expenditures (Frank et al., 2002; Pekmezaris et al., 2002). Hence, there appears to be both an unmet health- and economic need to prevent constipation in institutionalized elderly. Anticipating a rapid growth in the number of elderly, it is vital that these patient needs are safeguarded. Probiotic intervention could benefit constipated elderly, as probiotic bacteria are capable of modulating and balancing the gut microbiota (Hemarajata & Versalovic, 2013). They reportedly promote gut health during their transient passage through the gastrointestinal tract (Silvi et al., 2014), improving whole gut transit time, stool frequency and stool consistency in constipated individuals (Dimidi et al., 2014). In addition, probiotics have an excellent safety profile with few reported adverse events (Borriello et al., 2003; Gueimonde et al., 2004; Van den Nieuwboer et al., 2014a; Van den Nieuwboer et al., 2014b; Van den Nieuwboer et al., 2015a; Larsen et al., 2017). Despite their potential, however, probiotics are often not prescribed by elderly care physicians (Flach et al., 2017a). It appears that the probiotic innovation cycle in elderly care is significantly hampered, particularly in the industry development discourse (Larsen et al., 2017). During this phase, it is vital that product safety, efficacy and affordability is ascertained (Van den Nieuwboer et al., 2016). Therefore, we have recently reviewed the safety and efficacy of probiotic intervention (Larsen et al., 2017), but the economic impact with regard to bowel habit improvement remains
to be determined. It is crucial this impact is reviewed, as a substantial increase in
treatment expenditures, associated with the introduction of a novel intervention,
is likely to hamper the adoption of that intervention (Colón-Emeric et al., 2007)
regardless of potential benefits on health-related quality of life. The economic
impact is subject to the costs of the intervention but also depends on the probiotic
treatment effect. For instance, effective probiotic supplementation may alleviate
the overall economic burden for the institution, as the constipation prevalence and
the associated (conventional) treatment expenses are reduced.

We therefore set out to investigate the economic potential of probiotic supplemen-
tation in a nursing home setting with regard to constipation management. To this
end, we will first determine the probiotic lower efficacy limit required to reduce
the institution’s constipation-related expenses, after which we will estimate the
probiotic treatment effect based on a meta-analysis of current clinical evidence.

5.3 METHODOLOGY

5.3.1 Model

In order to meet the research objective of the present study, a mathematical model
is proposed that describes a situation where all nursing home residents receive
daily probiotic supplementation. In this model, the total constipation-related ex-
penses ($C_T$) are determined by conventional treatment expenditures without pro-
biotic supplementation ($C_{WPS}$), the probiotic supplementation costs ($C_{PS}$) and
the potential reduction in costs due to the efficacy of the probiotic intervention ($C_{R}$). A description of these variables and their interrelationship is provided below.

5.3.1.1 Conventional treatment without probiotic supplementation ($C_{WPS}$)

In the conventional setting (without daily probiotic supplementation), $C_{WPS}$ is de-
pendent on the conventional treatment costs ($C_C$), the constipation prevalence ($P$) and the number of residents ($N$). We differentiate $C_C$ into two components:
the costs of the pharmaceutical interventions ($C_{PT}$) and the costs associated with
the workload for nursing home employees ($C_{WL}$) (Equation 1). In this model, only
constipated nursing home residents receive conventional treatment.
5.3.1.2 Probiotic supplementation costs ($C_{PS}$)

In the novel (hypothetical) situation, all residents now receive daily probiotic supplementation. These costs need to be added to $C_{WPS}$, in order to determine $C_T$. However, a proportion of residents may already receive probiotic treatment, and no additional supplementation is provided to this group. Hence, $C_{PS}$ is determined by the probiotic product price ($C_{pp}$), the number of residents ($N$) and the fraction of non-probiotic-users ($P_{Nu}$) (Equation 2).

$$C_{PS} = C_{pp} \cdot N \cdot P_{Nu}$$  \hspace{1cm} (2)

5.3.1.3 Reduction in costs ($C_{R}$) due to probiotic efficacy ($E_{p}$)

The efficacy of the probiotic intervention ($E_{p}$) may reduce the overall economic burden for the institution, as fewer residents require conventional treatment for constipation in the new situation (depending on the effect size). $E_{p}$ is defined as the fraction of residents who, following probiotic supplementation, no longer require any (constipation-related) treatment, except for probiotic supplementation. $C_{R}$ is therefore a function of $E_{p}$ and $C_{WPS}$ (Equation 3).

$$C_{R} = C_{WPS} \cdot E_{p}$$

$$C_{R} = (C_{PL} + C_{WL}) \cdot N \cdot P \cdot E_{p}$$  \hspace{1cm} (3)

5.3.1.4 Total costs with probiotic supplementation ($C_{T}$)

In order to determine the new total costs, $C_{PS}$ needs to be added to $C_{WPS}$, and $C_{R}$ needs to be subtracted from the total. $C_{T}$ can thus be calculated as follows, when we insert all previous equations:

$$C_{T} = C_{WPS} + C_{PS} - C_{R}$$
5.3.1.5 Relative cost reduction ($S$)

When we compare the conventional situation (without supplementation) with the hypothetical novel situation, it allows us to determine the economic potential of daily probiotic supplementation, as the ratio between the two determines relative reduction in costs ($S$) (Equation 5). If $S < 1$, then probiotic supplementation reduces the overall economic burden of chronic constipation in a nursing home setting. If $S > 1$, then probiotic supplementation increases the overall economic burden. If $S = 1$, then the conventional treatment expenditures are equal to the total new costs, which we will refer to as the breakeven point.

$$S = \frac{C_T}{C_{WPS}}$$

$$S = \frac{(C_{PI} + C_{WL}) \cdot N \cdot P \cdot (1 - E_P) + (C_{PP} \cdot N \cdot P_{NU})}{(C_{PI} + C_{WL}) \cdot N \cdot P}$$

$$S = (1 - E_P) + \frac{(C_{PP} \cdot P_{NU})}{(C_{PI} + C_{WL}) \cdot P}$$  \hspace{1cm} (5)

5.3.1.6 The probiotic efficacy limit

By rewriting equation 5, the definition of $E_P$ can be obtained:

$$E_P = 1 - S + \frac{(C_{PP} \cdot P_{NU})}{(C_{PI} + C_{WL}) \cdot P}$$  \hspace{1cm} (6)

At the breakeven point, $S = 1$, and hence $E_P$ can be given by:

$$E_P = \frac{(C_{PP} \cdot P_{NU})}{(C_{PI} + C_{WL}) \cdot P}$$

With, $0 \leq E_P \leq 1$ \hspace{1cm} (7)
In this case, $E_P$ equals the minimum required probiotic efficacy to reduce the institution’s constipation-related expenses. In the present study, we will determine all previously discussed variables (summarized in Table 5.1) in order to calculate the minimum required $E_P$. $N$ is set at 100 in all following calculations, which is representative of an average-sized nursing home (Wilson et al., 2017). However, each variable (e.g. the constipation prevalence) can be manually adjusted to reflect the specific characteristics of any given nursing home. Furthermore, the primary outcome parameter ($E_P$) is independent from $N$ in our model, as can be seen in equation 6 & 7.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>$C_T$</td>
<td>Total constipation-related expenses</td>
</tr>
<tr>
<td>$C_{WPS}$</td>
<td>Total conventional treatment expenses without probiotic supplementation</td>
</tr>
<tr>
<td>$C_{PS}$</td>
<td>Probiotic supplementation costs</td>
</tr>
<tr>
<td>$C_R$</td>
<td>Reduction in costs due to $E_P$</td>
</tr>
<tr>
<td>$C_C$</td>
<td>Conventional treatment costs</td>
</tr>
<tr>
<td>$C_{PI}$</td>
<td>Pharmaceutical intervention costs</td>
</tr>
<tr>
<td>$C_{WL}$</td>
<td>Labour costs (workload)</td>
</tr>
<tr>
<td>$N$</td>
<td>Number of residents (set at 100)</td>
</tr>
<tr>
<td>$I$</td>
<td>Constipation Prevalence</td>
</tr>
<tr>
<td>$P_{NU}$</td>
<td>Fraction of non-probiotic users</td>
</tr>
<tr>
<td>$E_P$</td>
<td>Probiotic efficacy</td>
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</tbody>
</table>

### 5.3.2 Survey

A digital survey was developed for nursing home employees to gain insight into the aforementioned variables. The questionnaire was created using the SurveyMonkey® software and compromised 10 closed- and 4 open questions. Demographics, constipation prevalence, treatment advice, treatment frequency, probiotic advice,
reasons not to advise and the time spent on constipated clients were addressed. The survey questions were pilot tested with two elderly care physicians and two registered nurses, whose feedback was incorporated into the questionnaire before being sent to participants.

The online survey invites were sent to 521 Elderly Care Physicians (ECP) and 80 nursing homes in The Netherlands. Within nursing homes, surveys were circulated to ECP, Advanced Practice Nurses (APN), Registered Nurses (RN) and Nursing Assistants (NA). The healthcare professional databases of BSL-Springer and “Zorgkaart Nederland” were used to construct a contact information list. Additionally, a small subset of participants filled out the questionnaire during the “Geriatric Giants” conference in Maastricht, the Netherlands, on April 20th, 2017.

5.3.3 Literature search

A literature search was conducted to review the clinical efficacy of probiotic intervention and estimate the probiotic treatment effect. All studies reporting the effect of probiotic intervention in elderly nursing home residents on at least one of the Rome IV criteria for constipation (Sood & Ford, 2016) were eligible for inclusion in the present study. The online database of PubMed and Embase were utilized, using the following search terms: (Constipation [title/abstract] OR bowel movement* [title/abstract] OR bowel habit* [title/abstract]) AND (geriatric* [title/abstract] OR retired [title/abstract] OR institutionalized [title/abstract] OR “long-term care” [title/abstract] OR “nursing home*” [title/abstract] OR “residential home*” [title/abstract] OR aged-care [title/abstract] ) AND (probiotics [title/abstract] OR lactobacilli [title/abstract] OR bifidobacteria [title/abstract]) NOT review [ptyp].

5.3.4 Quantitative Data Synthesis

As the included studies utilized different probiotic strains and carrier matrices, the true treatment effect may vary from study to study (Flach et al., 2017b). We therefore used a random effects model to estimate the probiotic treatment effect. Individual studies are weighted based on their inter- and between study variance (Borenstein, Rothstein, & Cohen 2005). Both randomized and nonrandomized trials are included, and their variance is determined according to methods described by Devore & Berk (2007). The weighted mean difference between groups and a 95% confidence interval (CI) of its standard error were used as an indicator of effect size for our primary outcome parameters with regard to constipation. If pre-post
measure correlations were not provided in the included studies, we assumed a conservative estimate of $r = 0.7$ (following the recommendations by Rosenthal, 1993). Heterogeneity was assessed using Cochran’s Q.

The data were categorized in a Microsoft Excel (2010) spreadsheet (Microsoft, San Francisco, CA, USA) and analysed using the Metafor package in R Statistical Software (Viechtbauer, 2010; R Core Team, 2013). Values are reported as means and standard deviations, or means and 95% CIs of the standard error, unless specified otherwise. Calculation details are provided in the online Appendix.

### 5.4 RESULTS & DISCUSSION

#### 5.4.1 Survey respondents' characteristics

A total of 211 respondents completed the online survey between April 15th and May 15th, 2017. Of these respondents, 93 were excluded from data-analysis as they either did not meet the inclusion criteria ($N = 37$) or did not complete the questionnaire ($N = 56$). Hence, 118 responses of Dutch nursing home employees were included in the data-analysis of the present study, compromising; 50 ECP (42%), 7 APN (6%), 25 RN (21%) and 36 NA (31%). The demographics of survey participants are presented in Table 5.2.

<table>
<thead>
<tr>
<th>Table 5.2 Survey Participant Characteristics</th>
<th>N with corresponding %</th>
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<tbody>
<tr>
<td><strong>Specialization</strong></td>
<td></td>
</tr>
<tr>
<td>Elderly Care Physician</td>
<td>50 (42%)</td>
</tr>
<tr>
<td>Advanced Practice Nurse</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Registered Nurse</td>
<td>25 (21%)</td>
</tr>
<tr>
<td>Nursing Assistant</td>
<td>36 (31%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 30 years</td>
<td>22 (19%)</td>
</tr>
<tr>
<td>31-50 years</td>
<td>46 (39%)</td>
</tr>
<tr>
<td>51-64 years</td>
<td>49 (42%)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Years of practice</strong></td>
<td></td>
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<td></td>
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</table>
### 5.4.2 The conventional treatment expenditures ($c_{WPS}$)

First, we set out to determine the conventional treatment expenditures based on the quantitative data obtained from nursing home employees (NHE). In this section, we will therefore determine the corresponding values of $P$, $C_{PI}$ and $C_{WL}$.

| ≤ 10 years | 42 (36%) |
| 11-20 years | 39 (33%) |
| 21-30 years | 28 (23%) |
| ≥ 31 years | 9 (8%) |

<table>
<thead>
<tr>
<th>Sex</th>
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<tbody>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
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</tbody>
</table>

#### 5.4.2.1 Constipation prevalence ($P$)

In order to determine $P$, NHE were asked which percentage of their clients is chronically constipated. According to NHE in the present study, an average of ~48% of their residents is constipated and requires regular treatment (Figure 5.1, weighted average of 6,138 residents). This prevalence is lower than our earlier reported average of 62% (Larsen et al., 2017), but there are large differences between

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Figure 5.1. Half of nursing home residents are constipated.

This Figure portrays the reported prevalence of constipation in nursing homes, according to NHE (weighted average of 6,138 residents). The x-axis represents the percentage of constipated residents, the y-axis the percentage of respondents.
nursing homes. Nevertheless, these results demonstrate clearly that a substantial proportion of institutionalized elderly is constipated.

5.4.2.2 Pharmaceutical intervention ($C_{PI}$)

Subsequently, the conventional treatment regimens for constipation were reviewed. NHE were asked about the type and frequency of medication they generally administer to constipated clients. It appears that NHE in the present study most frequently administer osmotic laxatives to their constipated clients (65%). Bulk-forming laxatives, stimulant laxatives and rectal medication are administered to 20%, 21% and 22% of constipated residents, respectively (Figure 5.2, weighted average 6,138 residents). Probiotics are only administered to 10% of constipated residents (primarily due to a reported lack of knowledge (25%) and experience (30%)). Additionally, dietary adjustments are recommended to 35% (e.g. whole-wheat bread).

In order to determine $C_{PI}$, the average prices of these pharmaceutical interventions were obtained from the National Health Care Institute (NCHI, 2017), an advisory body of the Dutch government, and were multiplied by the corresponding weighted treatment frequencies (Figure 5.2). The price of a probiotic dose is valued at €0.35 in the present study, based on the average price of three commercially available probiotic products (Appendix: Table 1). Therefore, $C_{PI}$ required to treat a single constipated nursing home resident for a year amounts to €408 (Appendix: Table 2).

![Figure 5.2 Osmotic laxatives are frequently prescribed to constipated residents.](image)

This Figure portrays the frequency of treatments NHE administer to constipated residents (based on the weighted average of 6,138 residents). Osmotic laxatives are most frequently administered (65%) and probiotics are administered least often (10%).
5.4.2.3 Workload for personnel \((C_{WL})\)

NHE were then asked how much time is spent treating constipated resident, per department (or team), per week, in order to determine the associated personnel costs \((C_{WL})\). NHE indicated that an ECP spends on average 13 minutes, an APN 9 minutes, a RN 29 minutes and a dietician 16 minutes per week treating a constipated client. When we consider the average salaries of involved staff members, based on the wages of the National Career Guide (2017), we obtain an estimate of the personnel costs required to treat a single nursing home resident for constipation for a year: €1,669, excluding medication costs (Appendix: Table 3).

5.4.2.4 Total conventional treatment expenditures

When we combine \(C_{PI}\) with \(C_{WL}\), the costs required to treat a constipated nursing home resident for a year amount to €2,078. Hence, it would cost €100,145 annually to care for a hundred nursing home residents, solely regarding constipation, provided that \(P\) is 48% (Appendix: Equation 1). These results are in line with previous findings (Frank \textit{et al.}, 2002), both with regard to the total costs ($2,253 dollar US) and the ratio of \(C_{PI}\) to \(C_{WL}\) (1:5, respectively), and demonstrate the substantial economic burden of chronic constipation in nursing homes.

5.4.3 Probiotic supplementation costs \((C_{PS})\)

The second parameter we aimed to determine is \(C_{PS}\). For a single constipated resident, the probiotic supplementation costs amount to €129 per year, as \(C_{PP}\) is valued at €0.35 per dose (when calculated with non-rounded off values). However, in section 5.4.2.2, we also demonstrated that 10% of constipated residents already receives probiotic intervention. This group is excluded from \(C_{PS}\) in the present study. With \(P\) of 48% (section 5.4.2.1), \(P_{NU}\) therefore amounts to 95%. Hence, for 100 nursing home residents, \(C_{PS}\) amounts to €12,251 per year (Appendix: Equation 2).

5.4.4 The lower probiotic efficacy limit \((E_{p})\)

Now that we have determined \(C_{WPS}\) (section 5.4.2: €100,145) and \(C_{PS}\) (section 5.4.3: €12,251), we are able to determine the lower \(E_{p}\) limit required to reduce the institution’s constipation-related expenses (Appendix: Equation 3). When \(C_{WPS}\) is equal to \(C_{T}\) \((S = 1)\), the corresponding \(E_{p}\) is the minimum required efficacy limit (the breakeven point).
Figure 5.3 Probiotics reduce treatment expenditures when the constipation prevalence decreases by more than 12%.

This Figure portrays the following situations: 1) the costs of treating 100 nursing home residents for constipation without daily probiotic supplementation (prevalence 48% or 62%) and 2) the same situation with daily probiotic supplementation. On the x-axis, the hypothetical probiotic efficacy for the prevention of constipation is portrayed. On the y-axis, the total constipation-related expenses are portrayed. Line intersections represent break-even or equilibrium points. Green colored areas are profit zones. *The constipation prevalence is 62%. **The constipation prevalence is 48%.

We calculate that in a nursing home with 100 residents and \( P \) of 48%, daily probiotic supplementation may reduce the constipation-related treatment expenditures of the institution, when the probiotic intervention lowers \( P \) by more than 12.2% (Figure 5.3). From this point onwards, the treatment and care expenditures of the institution may be reduced substantially.

However, it should be noted that prevalence \( P \) may differ vastly between nursing homes. For instance, Larsen et al (2017) reports that the average \( P \) in a nursing home setting is ~62%, with broad inter-institution variations. A higher constipation prevalence requires lower \( E_P \) to reduce constipation-related expenses. For example, at 62%, the required \( E_P \) limit is reduced to 9.3% (Figure 5.3). Hence, the decision to provide probiotic supplementation to nursing home residents, from a financial point of view, should be accompanied by an appraisal of both \( E_P \) and \( P \) (Figure 5.4). When all nursing home residents are constipated, the intervention should reduce the prevalence by at least be 5.5%, to offset the costs of probiotic supplementation (Figure 5.4, \( P = 100\% \)).


**Figure 5.4 Probiotic efficacy & the constipation prevalence determine the economic potential of probiotic supplementation.**

This Figure portrays the minimum required probiotic efficacy limit to reduce constipation-related expenses of the institution. Probiotic efficacy is set off against the constipation prevalence. A high constipation prevalence requires relatively low probiotic efficacy to reduce constipation-related expenses. Green colored areas represent profit zones.

### 5.4.5 Probiotic efficacy in clinical research

Here we estimate the probiotic treatment effect based on the current clinical evidence of probiotics for the treatment or prevention of constipation in institutionalized elderly. To this end, we conducted a meta-analysis on the two most frequently reported outcome parameters with regard to constipation: defecation frequency and stool consistency. A total five clinical trials were identified that report the effects of probiotic intervention on either of these outcome parameters. An overview of the study designs and accompanying interventions is portrayed in Table 5.3.

#### 5.4.5.1 Defecation frequency

All studies report the effects of probiotic intervention on the defecation frequency of institutionalized elderly. The study by Pitkälä et al (2007) had the most participants (N = 209), and reported a significant increase in the percentage of days with defecations in both the BB-12 (36.0% ± 13.1%, p = 0.038) and the *B. Longum* group (38.8% ± 15.3%, p = 0.021), compared to control (30.6% ± 14.4%).
Table 5.3 Clinical trials with a probiotic intervention in institutionalized elderly reporting effects on constipation status

<table>
<thead>
<tr>
<th>Study:</th>
<th>Treatment:</th>
<th>Intervention period:</th>
<th>Subjects:</th>
<th>Design:</th>
<th>Outcomes included in present study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>An et al (2017)</td>
<td>L. acidophilus, Pediococcus pentosaceus and B. longum (6.0 x 10^11 CFU/g)</td>
<td>2 weeks</td>
<td>19 elderly nursing home residents with constipation</td>
<td>Single arm</td>
<td>Defecation frequency, stool consistency</td>
</tr>
<tr>
<td>Ouwehand et al (2002)</td>
<td>1) Control, 2) L. rhamnosus LC705 + P. freudenreichii shermanii JS (1–4 x 10^8 CFU/ml)* or 3) L. reuteri ING1 (3.6 x 10^6 CFU/ml)**</td>
<td>4 weeks</td>
<td>28 nursing home residents with reported difficulties in defecation (12 Rela®, 10 Bioprofit®, and 6 control patient)</td>
<td>Open label, 3 parallel groups</td>
<td>Defecation frequency</td>
</tr>
<tr>
<td>Pitkälä et al (2007)</td>
<td>1) Control, 2) Bifidobacterium longum strains (10^9 CFU/day) or 3) Bifidobacterium lactis BB-12 (10^9 CFU/day)</td>
<td>7 months</td>
<td>209 nursing home residents (51 control, 46 BB-12, and 82 B. Longum patients were included in the analysis)</td>
<td>Double-blind, placebo-controlled, 2 parallel groups</td>
<td>Defecation frequency, stool consistency</td>
</tr>
<tr>
<td>Van den Nieuwboer et al (2016)</td>
<td>Lactobacillus casei Shirota (6.5 x 10^9 CFU)</td>
<td>6 weeks</td>
<td>135 frail elderly nursing home residents (44 in analysis)</td>
<td>Single arm</td>
<td>Defecation frequency, stool consistency</td>
</tr>
<tr>
<td>Yeun and Lee (2015)</td>
<td>Non- or double-coated B. bifidum, B. lactis, B. longum, L. rhamnosus, L. acidophilus, and S. thermophilus (2.5-5 x 10^8 CFU/day)</td>
<td>2 weeks</td>
<td>40 constipated nursing home residents (20 per arm)</td>
<td>Double-blind, 2 parallel groups (two probiotic arms)</td>
<td>Defecation frequency, stool consistency</td>
</tr>
</tbody>
</table>

*Bioprofit®, **Rela®
In the study by An et al (2017), probiotic intervention increased the average defecation frequency of participants by 0.4 days per week, from 3.3 (±2.5) at baseline to 3.73 (±1.87) after the intervention. The results were, however, not significant (p = 0.676, N = 19). The study by van den Nieuwboer et al (2016) also reported a nonsignificant increase in the average defecation frequency per week after probiotic supplementation (5.2 ± 1.5 at baseline compared to 5.4 ± 1.7 after the intervention, p = 0.236). However, when we compare the defecation frequency of van den Nieuwboer et al (2016) with the other studies reviewed here, it appears that their mean defecation frequency at baseline was higher than the average defecation frequency of the other studies after probiotic supplementation (Figure 5.5), which could explain the relatively low observed treatment effect. In the open-label study by Ouwehand et al (2002), the effects of two probiotic products (Bioprofit® and Rela®) were compared with control and baseline. In the Rela® group, a significant increase in the average defecation frequency was observed compared with control (1.7 ± 0.5 vs. 2.8 ± 1.3, p < 0.05), however, no difference was observed compared with baseline (2.8 ± 1.5 vs. 2.8 ± 1.3). In the Bioprofit® group, on the other hand, a significant increase was observed compared with baseline (2.1 ± 0.9 vs. 2.6 ± 1.0, p < 0.05), but the results were only near significant compared with control (1.7 ± 0.5 vs. 2.6 ± 1.0, p = 0.065). As there was a relatively large difference in defecation frequency of the Bioprofit® and control group at baseline (2.8 ± 1.5 vs. 2.2 ± 1.4, respectively), and due to the reduced defecation frequency of the control group after the intervention period (from 2.2 ± 1.4 to 1.7 ± 0.5), we will only use the baseline comparisons of Ouwehand et al (2002) in our analysis (Figure 5.5). Lastly, the study by Yeun and Lee (2015) reported that a double-coated probiotic intervention significantly increased the defecation frequency of participants, median of which was increased from 3.0 [1.5, 7.8] at baseline to 5.0 [3.1, 8.8] after the intervention (p = 0.01).

Overall, it appears that probiotic supplementation increases the average defecation frequency of nursing homes residents by 13% [7.1%, 19.0%], or by Δ0.38 days per week [0.21, 0.56], from 2.95 at baseline to 3.33 after the intervention (Z = 4.27, p < 0.0001, Figure 5.5).

5.4.5.2 Stool consistency

Four studies report the effects of probiotic supplementation on stool quality or consistency of nursing home residents.
Probiotics increase defecation frequency of institutionalized elderly by 13%.

Figure 5.5 Probiotics increase defecation frequency of institutionalized elderly by 13%.

This Figure portrays the results of a random effects analysis on the defecation frequency of institutionalized elderly following probiotic supplementation. Values of Pitkälä et al (2007) are calculated from the percentage of days with bowel movements. Values of Yeun and Lee (2015) are estimated from the median and interquartile range according to the method described by Wan et al (2014).

According to van den Nieuwboer et al (2016), the percentage of constipation-like stools (type 1-2 Bristol Stool chart) decreased from 13.2% (±23.5%) at baseline, to 5.4% (±13.8%) after the intervention (p < 0.01). Similarly, Yeun and Lee (2015) reported that a double-coated probiotic intervention significantly reduced the number of hard and lumpy stools, median of which was decreased from 1 [0,1] at baseline to 0 [0,1] after the intervention (p < 0.05). In contrast, An et al (2017) reported a small but nonsignificant increase in the mean number of hard stools, from 0.47 (±1.06%) at baseline to 0.53% (±0.64%) after the intervention (p = 0.109). However, when we compare the results as the percentage of total stools, the difference becomes negligible (Figure 5.6). For the study by Pitkälä et al (2007), the percentage of constipation-like stools was estimated from the total number stools, and the percentage of ‘normal’ and ‘diarrhoea-like’ stools. It appears that there was a nonsignificant lower percentage of constipation-like stools in both the BB-12 (10.3% ± 19.0% vs. 13.4% ± 24.1%, p = 0.403) and the B. Longum group (12.6% ± 20.6% vs. 13.4% ± 24.1%, p = 0.884) compared with control.
Combined, it appears that probiotic supplementation decreases the percentage of hard and lumpy stools of nursing home residents by 40.3% [67.5%, 13.3%], or by Δ5.7% [9.6%, 1.9%], from 14.2% at baseline to 8.5% after the intervention (Z = -2.92, p < 0.005, Figure 5.6). Moreover, there was an overall significant increase in the percentage of normal stools (Z = 4.46, p < 0.0001) and a reduced percentage of diarrhoea-like stools (Z = -3.61, p < 0.0005).

### Figure 5.6 Probiotics reduce the percentage of constipation-like stools by 40%

This Figure portrays the results of a random effects analysis on the stool consistency of institutionalized elderly following probiotic supplementation. All values are portrayed (and converted when necessary) as the percentage of constipation-like stools. Values of Yeun and Lee (2015) are estimated from the median and interquartile range according to the method described by Wan et al (2014).

### 5.4.5.3 Sensitivity analysis

If pre-post measure correlations were not provided in the included studies, we assumed an estimate of $r = 0.7$ (following the recommendations by Rosenthal, 1993). The analyses were repeated with $r$ ranging from 0.3 to 0.9, to test the sensitivity of the results. The analyses indicated that the weighted mean differences between groups were equally similar (<10% difference) and significant (p < 0.01) with the adjusted pre-post correlations.
5.4.6 Economic potential of probiotic supplementation

In this section, we will evaluate how the previously discussed treatment effects on defecation frequency and stool consistency may correspond with the number of residents that are (no longer) constipated, and determine whether probiotics have the potential to reduce the economic burden of constipation in nursing homes.

5.4.6.1 Probiotic effects on constipation prevalence

To this end, we consult the Rome IV criteria for constipation (Sood & Ford, 2016), and use a defecation frequency of <3 per week, and hard or lumpy stool in at least 25% of defecations, as an indicator of having functional constipation (assuming other criteria for constipation are met). We can then estimate the number of residents with constipation from the weighted means and standard deviations as reported in Figure 5.5 & 5.6, if we assume a Gaussian distribution. We therefore calculate the number of standard deviations from the mean, required to meet the criteria for functional constipation, both pre- and post-supplementation, and estimate the proportion of residents with constipation from the corresponding Z-value (Hanley & McNeil, 1983). It appears that with regard to defecation frequency, approximately 51.2% of residents ‘are constipated’ prior to the intervention, compared with 41.3% after probiotic supplementation. Following the same analogy for stool consistency, a total of 32.6% of residents ‘are constipated’ prior to the intervention, compared with 18.5% after supplementation. When we consider the weighted means of these values, it allows us to make an assumption on the probiotic treatment effect. We therefore estimate that 42% of resident are constipated in the combined study population prior to probiotic supplementation, compared with 30% after the intervention, suggesting that $E_p$ is 28%.

5.4.6.2 Probiotic effects on the economic burden

Now that we have determined $E_p$, we can calculate the relative cost reduction $S$ and evaluate the economic potential of probiotic supplementation (Appendix: equation 4). Our results indicate that daily probiotic supplementation of all nursing home residents reduces the economic burden of chronic constipation in nursing homes, as $S < 1$. By subtracting $C_{WPS}$ from $C_T$, we show that in a nursing home with 100 residents and a constipation prevalence of 42%, the institution may save €12,595 annually (14% decrease) in constipation-related expenses (Appendix: equation 4).
However, there are various factors that influence the economic potential. For example, we used a probiotic product in our analysis with a cost of €0.35 per dose (section 5.4.3, \( N = 100 \)). When one strategically chooses the probiotic product, and replaces for instance regular milk / yogurt with a probiotic version, the additional costs of supplementation may be marginal. The total cost reduction may hence be increased with an additional €12,330 per year, depending on the overall costs of supplementation. Alternatively, we assumed in our model that a reduced constipation prevalence also reduces the laxative use by participants. However, this was not directly evident from the clinical studies, as there were no significant changes reported on the number of laxatives used (Ouwehand et al., 2002, Pitkälä et al., 2007; van den Nieuwboer et al., 2016). Little insight was provided in how the laxative prescription policies transpired in the nursing homes in question, and it remains uncertain whether laxative changes were more pronounced towards the end of the intervention period and whether the intervention periods were sufficiently long to capture subsequent changes (Ouwehand et al., 2002). If we assume that probiotics do not influence the laxative use of nursing home residents, the total cost reduction is lowered to €7,694 per year, but still reduces the overall economic burden. Finally, the cost of potential adverse events from (conventional) medication have not been taken into account in the present study, nor the fact that when constipation concerns diminish, elderly may increase their physical activity which in turn may further reduce constipation.

5.5 CONCLUSION AND RECOMMENDATIONS

We show that in nursing homes, where the prevalence of constipation and the associated economic burden is strikingly high, constipation-related expenses of the institution may be reduced through daily probiotic supplementation, as probiotic intervention lowers the constipation prevalence by 28% (without increasing diarrhoea). An average-sized nursing home, with 100 residents and a constipation prevalence of 42%, may therefore save between €8,000-€25,000 (9-28%) annually in constipation-related expenses when supplementing all its residents with probiotics.

To further substantiate the proposed economic potential of probiotic supplementation, however, additional research is warranted as the current study presents several limitations. First of all, the combined quality of the clinical evidence base of included studies is relatively low due to the lack of randomization, relatively short.
intervention periods, and the overall heterogeneity between studies (e.g. different strains, matrices and intervention periods). Our conclusions on the probiotic treatment effect therefore warrant cautious interpretation, and the true effect may vary between species and strains. Moreover, we assumed a linear relationship between reduced constipation prevalence and lowered treatment and care expenditures for the institution, but this relationship needs to be further substantiated. In this regard, it is recommended that the impact of probiotic intervention on the workload for nursing home employees is addressed in appropriately scaled and controlled future studies, as this has not been previously evaluated. Similarly, the effects of probiotic intervention on the laxative use by residents appears to be generally underreported, with little insight given into the course of treatments over time, and the prescription policy of the institution in general (e.g. evaluation periods and constipation criteria). We recommend that future studies take these factors into account when designing and reporting clinical studies, together with prophylactic effects of the intervention and the maintenance of reduced constipated status, in order to advance probiotic innovation and respond to the unmet health- and economic needs.

5.6 FURTHER CONSIDERATIONS

Our results only take into account the costs associated with constipation management, whereas probiotic supplementation may benefit the host in various other ways. For instance, probiotic supplementation may improve malnutrition status and prevent or treat diarrhoea in elderly nursing home residents (Hamilton-Miller., 2004; Rondanelli et al., 2015). We argue that probiotic supplementation could potentially reduce treatment expenditures in these areas as well, although this has not been previously reported. Therefore, our results could be the lower limit of the economic potential of probiotic supplementation in institutionalized elderly.

5.7 DISCLOSURE STATEMENT

E. Claassen is a consultant for several parties on probiotics, none of which are in direct conflict with the subject matter of this paper. O.F.A. Larsen is also Science Manager at Yakult Nederland B.V.
5.8 ONLINE APPENDIX MATERIAL

Appendices can be found online at: https://www.sciencedirect.com/science/article/pii/S2213434418300707?via%3Dihub#sec0165
5.9 REFERENCE LIST


