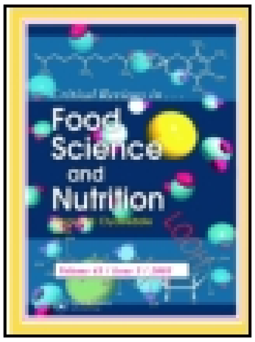

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REVIEW

Food or medication? The therapeutic effects of food on the duration and incidence of upper respiratory tract infections: a Review of the literature

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ABSTRACT

Purpose: Upper respiratory tract infections are common in children and adults. Antiviral treatments are only available for specific groups of patients, stimulating the distribution of over-the-counter medication to relieve the symptoms for the other patients. Studies about whole foods and their effect on the incidence and duration of upper respiratory tract infections were reviewed.
Methods: Randomized controlled trials and case-control studies available on MEDLINE, Web of Science, Cochrane Library and Embase were included.
Results and Conclusions: Thirty-three studies were included. The incidence of respiratory infections or symptoms was shown to be reduced in some studies when probiotics, prebiotics, growing-up milk, fish oil, kiwi, garlic and xylitol were taken. Duration was favorably influenced by the intake of elderberry, kiwi, probiotics and fish oil. When the risk of bias and repetition is taken into account, probiotics and elderberry repeatedly show favorable effects. Prudent conclusions can be made in selective patient groups. However, the studies were diverse and were only performed by a few study groups.

KEYWORDS
Whole foods; recurrent upper respiratory tract infections; probiotics; elderberry; kiwi

Introduction

Acute respiratory infections, including upper and lower respiratory infections, are the most common illnesses in children worldwide (Black et al. 2010), and also the main infectious reason that adults visit the emergency department (U.S. Department of Health and Human Services CfDCaP 2017). These infections are largely caused by viruses and are usually self-limiting. In severe infections, only a few antiviral drugs, like zanamivir or oseltamivir, are available for treatment. Since the infections are very common and only severe infections are treated with anti-viral drugs, most patients use over-the-counter drugs like cough sirup or painkillers to relieve the symptoms. However, are there also natural products, such as food, that can decrease the duration of the infection or influence the incidence of the infection?

In Chinese children, food intake has been shown to have an effect on respiratory infections. Mao et al. showed the relation of daily food intake and recurrent respiratory infections through the hair analysis of iron, zinc and copper levels. Children with the lowest levels of hair iron, zinc or copper, indicating a lower nutritional intake, showed more recurrent respiratory tract infections compared to healthy controls, according to this meta-analysis (Mao, Zhang, and Huang 2014). This study reflects the importance of adequate and varied nutrition over a long period of time in preventing respiratory tract infections.

Food synergy is defined as the combined action of health compounds within foods and of foods working together (Jacobs, Gross, and Tapsell 2009). This consists not of a single component but of multiple components, all influenced or not by each other. Food consists of macronutrients, i.e., fats, proteins and carbohydrates. Food also includes micronutrients like minerals and vitamins. Besides these well-known components, food also contains components like signal transducers, hormones, sterols, enzymes and enzyme inhibitors, polyphenols and fungicides, among others. These compounds are used by the plant or animal to stay alive and to protect itself against diseases or pathogens (Jacobs and Tapsell 2007). It is now believed that the phytochemicals in plant-based foods are responsible for beneficial health effects. Phytochemicals are plant-derived compounds, which are not considered essential for nutrition nor do they have nutritional value. Approximately 20,000 phytochemicals have been described in plants (Scalbert et al. 2011). Specific phytochemicals responsible for the color of a plant/vegetable or fruit, such as anthocyanins, carotenoids, lycopene or chlorophyll, are thought to have an effect on health (Gross 1991; Linus Pauling Institute OSU 2019). The principle of food synergy shows that the combined action of different nutrients has a greater biological effect than the sum of the biological effects acquired by individual nutrients (Yeum et al. 2009).

Different strategies in which food influences the human defence mechanism against pathogens has been previously

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described. Many berries and plants have antimicrobial compounds that can respond to microbial invasion and may modulate the bacterial microbiome when ingested. Berries like blueberries, lingonberries and cranberries have antibacterial effects against human pathogens (Heinonen 2007; Nohynek et al. 2006).

Other food components, such omega-3 fatty acids in oily fish or cod liver oil, have immunomodulatory capacities (Calder 2015). Another way in which food can be used as a defence against pathogens is to increase the amounts of antioxidants (kiwi) or to strengthen the local, innate or adapted immune system (probiotics). Xylitol can inhibit the growth of *Streptococcus pneumoniae* (Kontiokari, Uhari, and Koskela 1995), possibly via the fructose phosphotransferase system.

With this extended literature review, we describe evidence of the effect of natural everyday food on the duration and incidence of respiratory tract infections in children and adults. Reviews about single foods, like elderberry, probiotics, etc., can be found in the literature. However, to our knowledge, no reviews have been conducted about upper respiratory tract infections and the possible effects of different types of food groups on a specific infection. We did not include studies about supplements or single vitamins, since that does not reflect daily life situations. Instead, we included studies with whole food, pureed food or extracts to review the possible effect of food synergy.

Methods

Literature search and study selection

We systematically searched the Cochrane Library, MEDLINE, Embase and Web of Science up to November 2018. Studies on respiratory infections were identified with the search terms: "respiratory infections," "flu" and "common cold" (both as medical subject headings (MeSH) and free text terms). These were combined, using the set operator "AND", with the terms: "nutrition," "nutritional intervention," "natural food," "vegetables," "meat," "dairy," "fruits," "berries," "fish," "egg" or "oil" (MeSH or free text terms). Additional strategies for identifying studies included searching the reference lists of the articles included. Acute otitis media (AOM) is often seen as a complication of an upper respiratory tract infection (URTI), therefore, studies found on this subject were also included in this review (Figure 1).

Abstracts were screened for eligibility. Potential eligible studies were retrieved and read in full to assess whether they fulfilled all the inclusion criteria. Inclusion criteria were: (1) children aged 1–18 years or adults; (2) with respiratory tract infections or prone to respiratory infections; (3) not hospitalized or mechanically ventilated, but in an outpatient setting; (4) the food studied or products of that foodproducts group should be commercially available (e.g. in supermarkets); (5) the studies should be randomized controlled trials or non-randomized controlled trials.

The screening was conducted by two reviewers (EvdG and TH). Disagreement between the reviewers was resolved by consensus when possible, or by consulting a third reviewer to make the final decision.

Results

Study selection

A total of 2688 papers were identified, of which 179 were retrieved for full text review. After reading the full text, 150 studies were excluded (Figure 1). Tables 1–3 list the characteristics of the remaining 33 studies, which included 28 randomized controlled trials and 1 case-control trial, 1 pre-test-posttest design study and 3 Cochrane meta-analysis.

The clinical diversity between the studies was large with regards to the studied food and studied population. Therefore, the study data could not be compared for a meta-analysis. We evaluated all studies for the risk of bias (Table 4), and half of the studies had a low risk of bias.

Fruits

Orange juice. The oldest study concerning respiratory infections and fruit was conducted in 1979 and investigated how orange juice affected symptoms of the common cold. This study examined the effects of the daily intake of 180 ml of synthetic orange juice (no vitamin C added), synthetic orange juice with 80 mg artificial added vitamin C, or natural orange juice with 80 mg of natural vitamin C, in 362 young adults (ages 17–25 years) for a period of 72 days (Baird et al. 1979). Symptoms of the common cold were noted daily by the participants. The total symptoms recorded by the participants, the duration and number of episodes of illness in that winter period significantly favored both natural orange juice and synthetic orange juice with added vitamin C. Natural orange juice contains flavonoids as well as vitamin C. Other studies have indicated that flavonoids can modify the metabolism of vitamin C under defined experimental conditions (Wilson, Price-Jones, and Hughes 1976) and potentiate its nutritional activity. In the study from 1979, the effect of natural orange juice (containing both flavonoids and vitamin C) was not superior to that of synthetic orange juice which contained just high doses of vitamin C and no flavonoids. Vitamin C is known to stimulate the immune system (increase the activity of natural killer (NK) cells, lymphocyte proliferation, chemotaxis and as an antioxidant) as reviewed by the groups of Ran et al. (2018) and Wintergerst, Maggini, and Hornig (2006).

Kiwifruit. In mouse models, puree kiwifruit (gold) has been shown to enhance immune function by stimulating antigen-specific antibody production (total Ig and IgG) and the proliferation of mesenteric lymph node cells in the gut. Kiwifruit also modulates markers of innate immune function (phagocytosis, oxidative burst, T-cell activation, cytokine production and NK cells) (Hunter et al., 2008; Skinner et al. 2011). Two randomized crossover studies were performed using kiwifruit (and banana as control fruit) as the intervention for respiratory infections. For 32 healthy adults aged over 65 years, the intervention consisted of consuming four

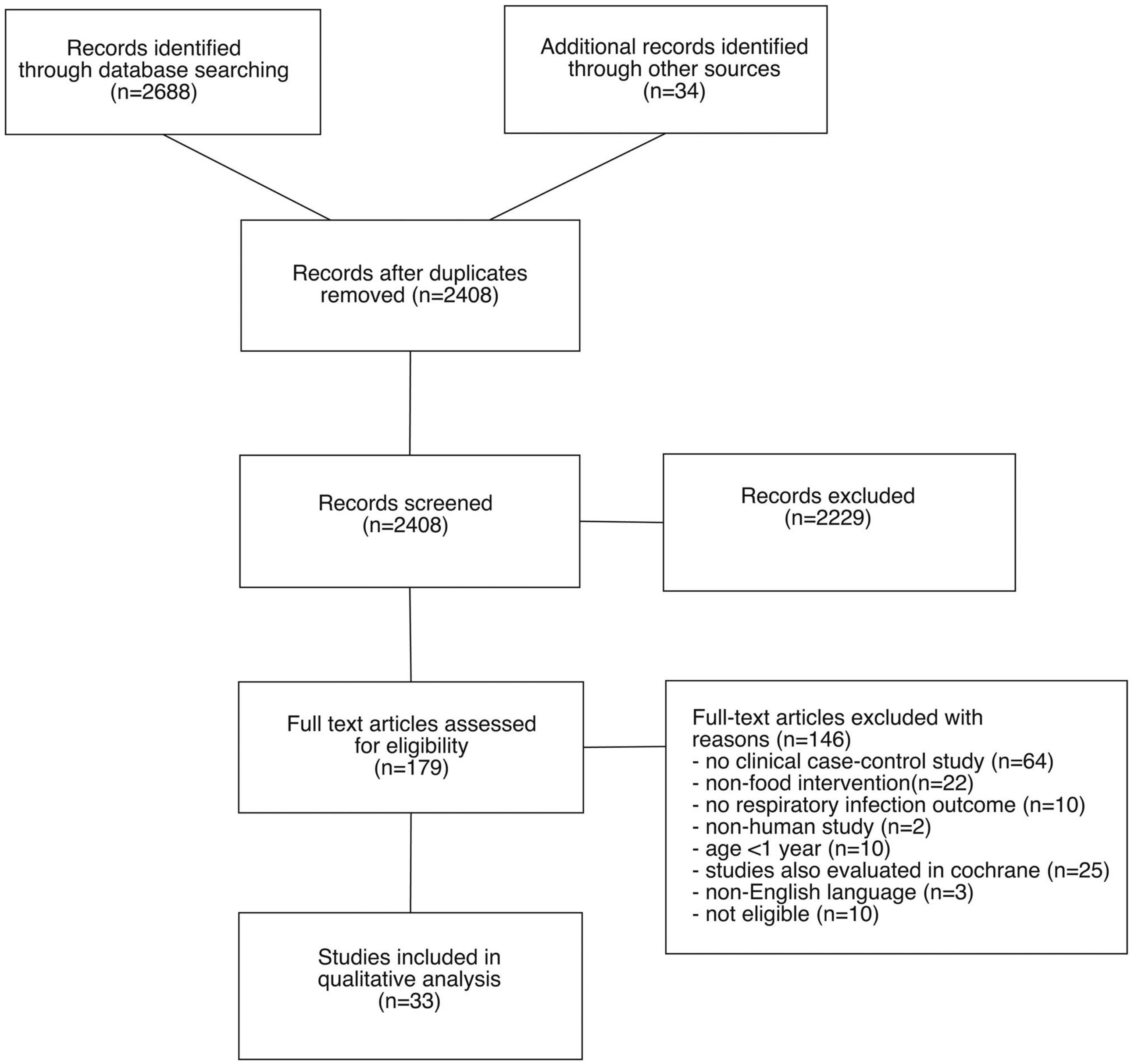

Figure 1. Inclusion flow chart.

gold kiwifruits or two bananas daily for four weeks. For 66 children aged 2–5 years, the intervention consisted of two gold kiwifruits or one banana, five days a week, also for four weeks.

In the adult population, the incidence of URTI did not decrease in the kiwifruit period, but the symptoms during the respiratory tract infection were reduced. The severity and incidence of a sore throat and head congestion were reduced significantly.

The adult study was supported by laboratory research. Consumption of kiwifruit showed significantly higher blood levels of vitamin C, α-tocopherol, lutein/zeaxanthin and red blood cell folate compared to consuming bananas, therefore, suggesting that intake of vitamin-rich food can increase vitamin levels in humans and can strengthen the host by reducing infectious symptoms (Hunter et al. 2012).

For children, the clinical differences were even more evident. The odds of not having a cold- and flu-like illness was 1.8 times greater during the kiwifruit segment of the intervention compared to the banana segment of the intervention (Odds Ratio (OR) = 0.55; 95% confidence interval (CI) 0.32–0.94; $p = 0.03$). When the symptoms were scored on a severity scale (Canadian Acute Respiratory Illness Flu Scale, CARIFS), functional complaints (i.e. symptoms that measure the impact of disease on the child's day-to-day activity) improved most in the kiwifruit period ($p = 0.006$). During the kiwifruit period, the children had a better appetite, felt better, had more energy and cried less than the period in which they are bananas (Adaim 2010).

Cranberry. Cranberry juice has an effective preventive capacity against urinary tract infections (Kontiokari et al. 2001; Stothers 2002). Cranberries produce antimicrobial compounds such as proanthocyanidins. These proanthocyanidins are thought to act by inhibiting the adhesion of *Escherichia coli* to uroepithelial cells. However, do these antimicrobial

Table 1. Therapeutic effect of food on the incidence of upper respiratory tract infections.

Author, year, Country	Sample Size (n)	Age range (years)	Intervention	Method of data collection	outcome	Follow up (months)	OR, RR or p-value
Baird et al. 1979, UK	377	17–25	Orange juice	RCT	No effect on incidence between natural and synthetic orange juice	3 months	n.s.
Adaim 2010, New Zealand	66	2–5	Kiwi gold	RCT	Reduced risk having a flu or cold of 45%	3 months	*0.55 (0.32–0.94), $p = 0.03$
Kontiokari et al. 2005, Finland	304	1–7	Cranberry juice	RCT	No effect on incidence (11.1 vs 11.6 episodes/year)	3 months	−0.55 (-2.1–1.0), $p = 0.48$
Nantz et al. 2013, USA	54	21–50	Cranberry juice	RCT	No effect on incidence (21 vs 31 in 10 weeks)	2.5 months	$p = 0.282$
Tiralongo, Wee, and Lea 2016, Australia	312	>18	Elderberry extract	RCT	No effect on incidence (12 vs 17 episodes)	14 days	$p = 0.40$
Larmo et al. 2008, Finland	254	19–50	Sea buckthorn berry	RCT	No effect on incidence (185 vs 161 episodes)	3 months	RR 1.15 (0.90–1.48)
Hughes et al. 2011, USA	427	> 18	5.0 grams galactooligosaccharides	RCT	40% reduction in percentage of days with flu in normal weight adults	2 months	**$p = 0.0002$
Hao, Dong, and Wu 2015, Cochrane	1927	0–92	probiotics	Meta-analysis	Episodes of URTI reduced by 47%	0–12 months	**0.53 (0.37–0.76), $p < 0.001$
Chatchatee et al. 2014, 5 countries	767	1–2	Growing up milk	RCT	No effect on URTI	12 months	RR 0.91 (0.84–0.99), $p = 0.10$
Li et al. 2014, China	264	3–4	Growing up milk	RCT	53 vs 96 episodes	6 months	*$p = 0.04$
Pontes et al. 2016, USA	256	1–4	DHA, prebiotics and beta-glucan	RCT	No effect on incidence	6 months	$p = 0.938$
Thienprasert et al. 2009, Thailand	180	9–12	Fish oil	RCT	54.3 % (fish oil) vs 67.4% (placebo) of URTI and/or diarrhea	6 months	**$p = 0.006$
Malan et al. 2015, South Africa	321	6-11	DHA/EPA + iron	RCT	No effect on incidence compared to placebo	8.5 months	n.s
Linday et al. 2004, USA	94	0.–6-5	Cod liver oil and multivitamin-mineral	Case control	No effect on incidence (68 vs 61 episodes)	6 months	$p = 0.80$
Azarpazhooh, Lawrence, and Shah 2016, Cochrane	3405	< 12	xylitol	Meta-analysis	Reduction of Acute Otitis Media in healthy children from 30% to 22%	Few days to 3 months	*RR 0.75 (0.65–0.88)
Josling 2001 UK	146	> 18	Garlic	RCT	Episodes reduced 24 vs 65 episodes	3	**$p < 0.001$
Da Boit et al. 2015, UK	42	> 18	Fish oil, vitamin D and whey protein	RCT	No effect on incidence (45% vs 49% of participants reporting URTI)	3.5 months	n.s.
Garaiova et al. 2015, Slovakia	57	3–6	Probiotics, vitamin C and xylitol	RCT	Decrease of 49% of URTI	1.5 months	*$p < 0.05$
Calatayud et al. 2017, Spain	128	1–5	Mediterranean diet	Prospective Before-after	2.9-fold decrease in URTI incidence	12 months	**$p < 0.001$

RCT = Randomized controlled trial. URTI = Upper respiratory tract infections. n.s.= non-significant. OR = Odds Ratio.
*= $p < 0.05$;
**= $p < 0.01$

capacities also provide protection in respiratory tract infections? A randomized controlled trial was performed in 341 children aged 1–7 years who received five ml/kg (up to 300 ml) of cranberry juice or a placebo per day, for three months.

The number of respiratory infections and the duration of symptoms did not differ between the cranberry group and the placebo group (Kontiokari et al. 2005).

Oral bacterial carriage and the bacterial fatty acid composition in stools did not change, even though cranberries have been found to reduce the adhesion of some bacteria in vitro (Kontiokari et al. 2005).

Another randomized double-blind, placebo-controlled study was performed in 45 healthy adults. The subjects drank 450 ml/day of cranberry juice or a placebo for 10 weeks. In the cranberry group, the incidence of illness was not reduced, however, significantly fewer symptoms of cold and influenza were reported ($p = 0.031$). The duration of the illness, scored in days missed from work/school, did not differ between the two groups. Laboratory parameters

Table 2. Therapeutic effect of food on the duration of respiratory infections.

Author, year, country	Sample Size (n)	Age range (years)	Intervention	Follow up	Method of data collection	outcome	OR, RR, p-value
McLean Baird et al. 1979, UK	377	17–25	Orange juice	3 months	RCT	No difference between natural and synthetic orange juice	n.s.
Hunter et al. 2012, New Zealand	37	> 65	Kiwi gold	5 months	RCT, crossover	Reduction of sore throat (2.0 vs 5.4 days) and head congestion (0.88 vs 4.69 days)	*$p = 0.024$ and $p = 0.029$, respectively
Kontiokari et al. 2005, Finland	304	1–7	Cranberry juice	3 months	RCT	No effect on duration (8.7 vs 9.4 days)	−0.7 (-3.4–1.9), $p = 0.46$
Tiralongo, Wee, and Lea 2016, Australia	312	>18	Elderberry extract	14 days	RCT	Shorter duration of URTI days (57 vs 117 days)	*p=0.02
Zakay-Rones et al. 1995, Israel	27	5–56	Daily 4 x15 ml elderberry sirup (adults) 2x15 ml (child)	6 days	RCT	2.7 days (elderberry) vs 4.0 days (placebo)	**$p < 0.001$
Zakay-Rones et al. 2004, Norway	60	18–54	Elderberry sirup	10 days	RCT	2–3 days (elderberry) vs 6 days (control)	**$p < 0.001$
Kong 2009, China	64	16–60	Elderberry extract	2 days	RCT	Fever disappeared after 48 hours in 100% of elderberry group vs 22% in placebo	**$p < 0.001$
Larmo et al. 2008, Finland	254	19–50	Sea buckthorn berry	3 months	RCT	No effect on duration (4 vs 3 days)	RR 1.05 (0.87–1.27)
Hao, Dong, and Wu 2015, Cochrane	831	18–92	probiotics	3.0–8.5 months	Meta-analysis	Reduction of -1.89 days	**-2.03 to -1.75, $p < 0.001$
Li et al. 2014, China	264	3–4	Growing up milk	6 months	RCT	3.5 days (GU milk) vs 4.3 days	**$p = 0.007$
Thienprasert et al. 2009, Thailand	180	9–12	2 grams fish oil 5 days a week	6 months	RCT	2 days (fish oil) vs 4 days (placebo) URTI and/or diarrhea	*$p = 0.024$
Malan et al. 2015, South Africa	321	6-11	DHA/EPA + iron	8.5 months	RCT	No effect on duration compared to placebo	n.s.
Lissiman, Bhasale, and Cohen 2014, Cochrane	146	> 18	Garlic	3	1 RCT Cochrane	Duration 4.63 vs 5.63 days	$p > 0.05$

*= $p < 0.05$;
**= $p < 0.01$

showed the improved ability of gamma delta ($\gamma\delta$) T cells to proliferate in culture after the adults took the cranberry juice, as well as lower the production of an inflammatory cytokine, interleukin 6 (IL-6) (Nantz et al. 2013).

Elderberry. Elderberry, or *Sambucus nigra* L., has been used in folk medicine as a remedy for the common cold and influenza (Association BHM 1983). Elderberry is reported to contain high doses of flavonoids and has antiviral (Roschek et al. 2009), antioxidant, anti-inflammatory and immune-modulating capacities (Badescu et al. 2015). It contains anthocyanins, which are considered to be the active component of the elderberry (Mikulic-Petkovsek et al. 2015). Besides these components, elderberries are rich in vitamins (A, B1, B2, B6, B9, C and E), trace elements, minerals and phytochemicals, such as carotenoids, phytosterols and polyphenols (Tiralongo, Wee, and Lea 2016).

Holst et al. reviewed the efficacy of elderberry extract in pregnant women. All clinical studies ($n = 3$) included in this review showed improvement. Although the total number of patients using the elderberry extract from all three studies was only 77 (Holst, Havnen, and Nordeng 2014), symptoms were relieved significantly faster in all elderberry groups (Holst, Havnen, and Nordeng 2014).

When given as an oral sirup to 60 adult Norwegian patients with proven influenza A or B infection, the symptoms were relieved significantly earlier compared to the control group. The usage of painkillers and nasal sprays was also significantly less in the elderberry group (Zakay-Rones et al. 2004). A study in Panama showed that the same sirup also relieved the symptoms significantly earlier in 27 influenza B patients (Zakay-Rones et al. 1995).

In China, 64 patients with flu symptoms were also treated with elderberry extract. A quick improvement was seen after 24 h in four of six symptom scores (headache, nasal congestion fever, muscle aches, but not cough or mucus discharge). After 48 h, all six symptoms improved in the elderberry group, whereas the symptoms worsened in the placebo group (Kong 2009).

In 312 economy class air travelers, the risk of developing a respiratory infection was present due to stressful circumstances and air conditioning. When the travelers took 300 mg of elderberry extract 10 days prior to their overseas travel until 4 days after arrival, the incidence was not

Table 3. Probiotic RCTs after the Cochrane meta-analysis.

Author, year, Country	Sample Size (n)	Age (years)	Probiotics	Species	Method of Data Collection	Outcome	FU (months)	OR, 95% CI
Langkamp-Henken, B, 2015, USA	581 stressed students	20	3 different probiotics or placebo	*Bifidobacterium longum* and *bifidum, Lactobacillus helveticus*	RCT	1 probiotic showed decreased incidence	1.5	*$p < 0.05$
Hojsak et al. 2016, Croatia	210 healthy day care children	1–6	Probiotics or placebo	*BB-12*	RCT	No effect on incidence No effect on duration	3	95% (0.25-0.38) $p = 0.992$ (Incidence) $p = 0.740$ (duration)
Shida et al. 2017, Japan	96 healthy office workers	30–49	Probiotics or control milk	*Lactobacillus casei*	RCT	lower incidence 22.4 vs 53.2% shorter duration 2.8 vs 5.0 days	3	*$p = 0.002$ *$p = 0.002$
Kalima K, 2016, Finland (Kalima et al. 2016)	983 Military	> 18	Probiotics or placebo	*Lactobacillus rhamnosus, Bifidobacterium lactis*	RCT	No effect on incidence No effect on duration	5	n.s.
Gerasimov et al. 201622Ukraine	315 sick family members	3–12	Probiotics and prebiotics or placebo	*Lactobacillus acidophilus, Bifidobacterium lactis*	RCT	No effect on incidence Shorter duration 5.0 vs 7.0 days	0.5	$p = 0.261$ **$p < 0.001$
Strasser et al. 2016, Austria	33 trained Athletes	20–35	5 different probiotics or placebo	*Bifidobacterium bifidum* W23 and *lactis* W51, *Enterococcus faecium* W54, *Lactobacillus acidophilus* W22 and *brevis* W63, *Lactococcus lactis* W58	RCT	Incidence decreases 2.2-fold	3	*$p = 0.02$
Prodeus et al. 2016, Russia	599 healthy day care children	3–6	Probiotics or control milk	*Lactobacillus casei*	RCT	Incidence reduction of 18.45%	4	95% (0.69-0.96) *$p = 0.017$
Pu et al. 2017, People's Republic of China	205 healthy volunteers	> 45	Yoghurt with probiotics or normal diet	*Lactobacillus paracasei*	RCT	Lower incidence 35.7 vs 51.0%	3	*$p = 0.030$
Nocerino et al. 2017, Italy	377 healthy day care children	1–4	Fermented cow's milk or fermented rice or placebo	*Lactobacillus paracasei*	RCT	Lower risk in fermented cow's milk -22% Lower risk in fermented rice -12%	3	**$p < 0.001$ $p = 0.05$

*= $p < 0.05$;
**= $p < 0.01$

Table 4. Risk of bias. The studies of Catalayud et al. and Linday et al. were not included since they are not RCTs. The 3 Cochrane meta-analyses were also not included.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome and assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Adaim 2010	⊕	⊕	–	–	⊕	⊕
Chatchatee et al. 2014	⊕	⊕	⊕	⊕	⊕	⊕
Da Boit et al. 2015	?	?	?	?	–	⊕
Garaiova et al. 2015	⊕	⊕	⊕	⊕	⊕	⊕
Gerasimov et al. 2016	⊕	⊕	⊕	?	⊕	⊕
Hojsak et al. 2016	⊕	⊕	⊕	⊕	⊕	⊕
Hughes et al. 2011	⊕	⊕	⊕	⊕	⊕	?
Hunter et al. 2012	–	–	–	–	⊕	⊕
Josling 2001	⊕	⊕	–	⊕	⊕	?
Kalima et al. 2016	⊕	⊕	⊕	⊕	–	⊕
Kong 2009	⊕	⊕	⊕	⊕	⊕	⊕
Kontiokari et al. 2005	⊕	⊕	⊕	⊕	⊕	⊕
Langkamp-Henken, 2015	⊕	⊕	⊕	⊕	?	⊕
Larmo et al. 2008	⊕	⊕	⊕	⊕	⊕	⊕
Li et al. 2014	⊕	⊕	⊕	?	⊕	⊕
Malan et al. 2015	?	⊕	⊕	⊕	?	⊕
Baird et al. 1979	?	?	⊕	⊕	⊕	?
Nantz et al. 2013	⊕	⊕	⊕	?	⊕	⊕
Nocerino et al. 2017	⊕	⊕	⊕	⊕	⊕	⊕
Pontes et al. 2016	⊕	⊕	⊕	⊕	⊕	⊕
Prodeus et al. 2016	⊕	⊕	⊕	⊕	⊕	⊕
Pu et al. 2017	⊕	⊕	–	?	⊕	⊕
Shida et al. 2017	?	?	?	?	⊕	⊕
Strasser et al. 2016	⊕	⊕	⊕	?	⊕	?
Thienprasert et al. 2009	?	?	⊕	?	⊕	⊕
Tiralongo, Wee, and Lea 2016	⊕	⊕	⊕	⊕	⊕	⊕
Zakay-Rones et al. 1995	⊕	⊕	⊕	?	–	⊕
Zakay-Rones et al. 2004	⊕	⊕	⊕	⊕	⊕	⊕

influenced, but the duration of the symptoms was influenced (Tiralongo, Wee, and Lea 2016).

Sea buckthorn berries. Sea buckthorn berries were investigated in 254 healthy volunteers in a double blind, randomized placebo-controlled trial because of their known immunomodulatory properties and positive effects on health. They contain flavonoids and polyphenolic compounds, which influence the immune system and inflammatory cells, and they have antimicrobial properties. The frozen sea buckthorn puree contained 16.7 mg of flavonol glycosides (mostly isorhamnetin) and low doses of vitamin C and E. No clinical effect was seen in the number or duration of respiratory tract infections in healthy volunteers (Larmo et al. 2008).

Dairy products, pre- and probiotics

Prebiotics. Prebiotics are defined as "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of a limited number of bacterial species in the colon" (Orrhage and Nord 1999). Prebiotics like galacto- and fructooligosaccharides aim to increase the load of lactobacilli and bifidobacteria to promote health in the host (Bouhnik et al. 1997). They also increase fecal short chain fatty acids, which have been associated with decreased epithelial permeability (Mariadason, Barkla, and Gibson 1997). In children, infant formula is usually supplemented with prebiotics, which is usually consumed by children younger than one year of age. These studies were excluded from this review since this age group was in the exclusion criterion. In adults, galactooligosaccharides are supplied in packets and can be mixed into any beverage. In the study by Hughes, 427 healthy students with stress due to their final exams took 2.5 or 5.0 g of prebiotics or placebo for eight weeks. There was no difference in the incidence of common cold or flu between the groups. However, galactooligosaccharide supplementation attenuated the cold/flu symptoms in specific groups (normal, healthy weight but not in obese subjects; moderately stressed but not at highly stressed) (Hughes et al. 2011).

Fermented dairy/probiotics. Probiotics are defined as "live microorganisms administered in adequate amounts which confer a beneficial physiological effect on the host". The natural mechanism of action for probiotics is fermentation, one of the oldest techniques for preserving dairy food, and their natural occurrence is therefore in fermented food (yoghurt, cheese). Nowadays, they are usually administered in milk products or in capsules. The exact mechanisms by which probiotics may improve health are not completely clear. There might be several mechanisms like immunomodulation of innate and acquired immunity, but also enhancement of local immunity (reviewed in Hao et al. (2011)). In our search, almost half of the articles about food and respiratory infections studied the effect of probiotics.

A Cochrane review in 2015, which involved 3720 participants, concluded that probiotics were better than a placebo in reducing the number of participants who experienced episodes of acute URTI by 47%. The mean duration of an episode of acute URTI was reduced by about 1.89 days; antibiotic use and cold-related school absences were also reduced. In children, the effect of reducing the number of episodes of URTI was greater than in adults, and almost no effect was seen in elderly people. The authors concluded that the results favor the probiotic group, however, the quality of the evidence was low or very low (Hao, Dong, and Wu 2015).

Since that review, nine articles that fit our inclusion criteria have been published about probiotics and respiratory infections. They are summarized in Table 3 (Hojsak et al. 2016; Gerasimov et al. 2016; Langkamp-Henken et al., 2015; Shida et al. 2017; Kalima et al. 2016; Nocerino et al. 2017; Strasser et al. 2016; Pu et al. 2017; Prodeus et al. 2016). In these studies, the study populations and the species of probiotics were different (Table 3).

Six of the nine studies showed a decreased incidence of URTI (Langkamp-Henken et al., 2015; Shida et al. 2017; Nocerino et al. 2017; Prodeus et al. 2016), while the other three studies showed no effect of the probiotics on incidence (Hojsak et al. 2016; Gerasimov et al. 2016; Kalima et al. 2016). The effect of the probiotics on duration was described in four of the nine studies. Two studies showed a decreased duration (Gerasimov et al. 2016; Shida et al. 2017), and the other two studies showed no effect on the number of days with symptoms (Hojsak et al. 2016; Kalima et al. 2016).

Most studies about probiotics are performed with single strain probiotics, but can mixtures with multiple strains have an additive positive effect? A few studies with multiple strains have been conducted. There are several indications for mixtures with multiple strains, however, evidence is lacking for their effect on respiratory infections (Chapman, Gibson, and Rowland 2011). One study that investigated a mixture of 12 strains in 1062 children found that the same reduction in doctors' visits and incidence of infections was described compared to single strains. Only a decrease in gastrointestinal infections was seen in the mixture group (Lin et al. 2009).

Follow-up/growing-up milk. Follow-up/growing-up milk can contain several added compounds and is usually given to children beyond the age of one year as a replacement for cow's milk. Chatchatee studied giving 767 healthy children, with a mean age of 1.5 years, 400–750 ml of growing-up milk alone or supplemented with prebiotic short-chain galactooligosaccharides (scGOS) and long-chain fructooligosaccharides (lcFOS) and with n-3 long-chain polyunsaturated fatty acids (LCPUFAs) for 52 weeks. The primary outcome, a decreased risk of at least one infection, was borderline significant. A trend toward a protective effect for respiratory infections by using growing-up milk was observed, though, not very strong despite the large number of participants (Chatchatee et al. 2014).

In China, Li et al. studied a combination of follow-up milk with docosahexaenoic acid (DHA), prebiotics (polydextrose and galactooligosaccharides) and yeast β-glucan in 264 children aged three to four years of age. In this group, there were fewer episodes and a shorter duration of acute respiratory infections (Li et al. 2014).

The same combination of supplements from the Chinese study was used in another study in Brazil, with a cow's milk-based beverage given to children one to four years of age. This group was younger, and the incidence of asthmatic disease in Brazil is higher than in the Asian population, which makes the studies less comparable with respect to the study population. In the 256 Brazilian children, there was no beneficial effect on the incidence of acute respiratory infections when children were given the supplemented drinks for 28 weeks (Pontes et al. 2016).

Fats

LCPUFAs, fish oil and cod liver oil. The LCPUFAs of interest include the omega-3 LCPUFAs, eicosapentaenoic acid (EPA) and DHA, and the omega-6 LCPUFA arachidonic acid (ARA), which are all synthesized endogenously from the precursors, alpha-linolenic acid (ALA, omega-3) and linoleic acid (LA, omega-6). LCPUFAs are important fatty acids for immune cells. There should be a balance between n-3 and n-6 LCPUFAs, in favor of n-3 LCPUFAs. Most Western diets have an imbalanced intake, with too much of the pro-inflammatory n-6 LCPUFAs. Increasing n-3 LCPUFAs should optimize the regulation, maturation and response of the immune system (Simopoulos 2002).

DHA, EPA and ARA serve as cell membrane components as well as precursors for several biologic mediators, and they have essential roles in inflammation and immune function (Calder 2015; Calder 2012). The human body cannot convert n-6 fatty acids to n-3 fatty acids or vice versa. Therefore, the major source of n-3 fatty acids comes from dietary sources.

In Thailand, 170 schoolchildren in aged 9–12 years were supplied with 2 g of either soybean or fish oil in their chocolate milk. Fish oil contains the (very long) long-chain n-3 PUFAs, EPA and DHA. In the case of this study, the children received 200 mg of EPA and 1 g DHA daily, for 6 months. Significantly fewer children who consumed fish oil experienced an illness, and the total days of illness was significantly lower in the fish oil group (two days compared to four days in the soybean-oil group, which is rich in n-6 LCPUFAs). The authors did not make a difference between diarrhea illnesses or respiratory infections. They mention that the illnesses were "mainly upper respiratory tract infections" (Thienprasert et al. 2009).

Malan et al. performed a study in 321 iron-deficient South African children, to investigate if fish oil (DHA/EPA) could have a beneficial effect. Iron supplementation in iron-deficient patients is known to reduce infectious morbidity due to the optimization of the immune system (de Silva et al. 2003; Tielsch et al. 2006). However, iron supplementation can also increase morbidity from infections because of the dependence of pathogenic microorganisms on iron (Cherayil 2010; Murray et al. 1978). When iron-deficient children were supplemented with iron, in combination with DHA and EPA, versus iron alone, the increase in infections because of the iron supplementation was attenuated compared to iron supplementation alone (Malan et al. 2015). However, children receiving only placebo supplementation showed lower incidence and shorter duration of URTI compared to all 3 supplemented groups (iron alone, DHA/EPA alone and DHA/EPA + iron). One possible mechanism for this outcome is the incorporation of DHA and EPA into the macrophage phospholipid bilayers, with improved phagocytosis and less extracellular iron, needed for pathogen growth, left unbound. Another mechanism could be DHA/EPA protection against iron-induced oxidative stress, with reduced immune cell damage and improved immune response (Appay and Sauce 2008).

Cod liver oil is a fish-derived oily product, which has been available for hundreds of years and contains vitamin A, vitamin D and long-chain omega-3 fatty acids. Cod liver oil was first described in 1932 by Holmes to reduce absenteeism from work because of colds and respiratory diseases (Holmes et al. 1932; Holmes, Sawyer, and Comstock 1936). No randomized trials could be found. In 2004, Linday et al. investigated the effect of supplementation with one teaspoon of cod liver oil and a multivitamin-mineral in 47 children with URTIs in a case control study. The total number of infections was not influenced by the cod liver oil. No data were available about the duration of the illness (Linday et al. 2004). Now, cod liver oil has been displaced by synthetic vitamins like vitamin D, with a more pleasant taste. However, a major source of fatty acids is lost with this replacement.

Other

Garlic. Garlic contains numerous compounds, some of which are known for their antimicrobial and antiviral properties that relieve the common cold. Garlic has been investigated in extracts, not as bulbs of garlic. The extract contains immunomodifying compounds like apigenin (a flavonoid), a Maillard reaction product, lectins and fructooligosaccharides, and it has been shown to improve the proliferation of T cells and NK cells (Nantz et al. 2012; Chandrashekar and Venkatesh 2009; Chandrashekar, Prashanth, and Venkatesh 2011). Eight studies were investigated for a Cochrane review, of which one met the inclusion criteria of both the Cochrane review and our own (Lissiman, Bhasale, and Cohen 2014; Josling 2001).

A garlic supplement (with 180 mg of allicin content) or placebo was administered to 146 participants that were randomly divided into two groups. The incidence and duration of the common cold decreased significantly in the garlic group (Josling 2001).

Xylitol. Xylitol is a polyol sugar alcohol, which can be produced from birch trees. Natural sources of xylitol include plums, strawberries, raspberries and rowanberries (Makinen 1980). Several studies have been performed with xylitol chewing gum and otitis media. In a Cochrane review (Azarpazhooh, Lawrence, and Shah 2016), the authors included four randomized controlled trials (RCTs) in a meta-analysis, of which three RCTs were with healthy Finnish children attending day care. They showed a reduced risk of AOM in these three RCTs, with a total of 1826 healthy children, with a relative risk of 0.75 (95% CI 0.65–0.88) (Hautalahti et al. 2007; Uhari, Kontiokari, and Niemela 1998; Uhari et al. 1996).

The other RCT included 1277 children, also Finnish, suffering from recurrent respiratory infections. In this group, xylitol did not reduce the occurrence of AOM (Tapiainen et al. 2002). Xylitol chewing gum was superior to xylitol sirup in preventing AOM in healthy children. The authors' conclusion was that there is fair evidence for a prophylactic administration of xylitol in healthy children attending day care centers to reduce the occurrence of AOM from 30% to 22%, but not in sick children or among otitis-prone children (Azarpazhooh, Lawrence, and Shah 2016).

Combinations. A combination of fish oil, vitamin D and wheat protein or a placebo drink was given to 42 female athletes for 16 weeks. There were no differences in the number of URTI episodes between the groups. When a URTI was present, there were no differences in either the severity or duration of the episodes. However, the total number of symptom days reported was significantly lower in the supplement group (Da Boit et al. 2015).

One study investigated the effect of a mixture of probiotics, xylitol and 50 mg vitamin C or a placebo (xylitol chewing gum) in 69 healthy children. In the intervention group, the incidence rate of URTI dropped 33% ($p = 0.002$) and the duration of days with symptoms also decreased with 51% ($p = 0.006$) (Garaiova et al. 2015).

Using a pretest-posttest design, Calatayud et al. investigated the effect of the Mediterranean diet in 128 children with recurring colds. The Mediterranean diet consisted of multiple food products (e.g. fresh fruits, vegetables, dairy products, fish, water, eggs and red meat in moderation) and advices (e.g. consuming unprocessed and locally produced foods, physical activity, etc.). The incidence rate dropped 2.9-fold ($p < 0.001$). Besides the lower incidence, favorable side effects were mentioned, such as decreased antibiotic use, emergency room and hospital admissions or complications of the infections (Calatayud et al. 2017).

Discussion

In this systematic review about whole foods and their effect on URTIs in children and adults, 33 studies were included. 28 of them were randomized controlled trials, 1 was a case control study, 1 was a pretest-posttest design and 3 were Cochrane meta-analyses. Studies with food products are difficult to investigate because of the possible introduction of bias (Table 4). Before conclusions can be drawn for the general public, multiple studies with significant favorable outcomes should be available. Most studies were single studies, only a few food products are investigated in multiple studies. However, the studies about probiotics, growing up milk and elderberries showed an overall low risk of bias and were investigated by several study groups.

To put whole foods into perspective, it is necessary to examine the effect of alternative treatments reported in the literature. Studies that investigated supplements also showed favorable results. A meta-analysis on vitamin C was nonconclusive due to heterogeneity of the studies. When extra therapeutic doses of vitamin C were added to routine supplements, it was able to shorten the duration by a small amount (Ran et al. 2018). The orange juice study suggests an effect of vitamin C supplementation (Baird et al. 1979). However, no consistent effect of vitamin C was seen on the duration or severity of colds in a Cochrane meta-analysis (Hemila and Chalker 2013). Trials with vitamin D supplements were not conclusive in terms of shortening the duration of viral URTIs, but most of them did not show any therapeutic effects (Yamshchikov et al. 2009). Zinc is an essential nutrient for normal function of the immune system. Supplementation of zinc appears to be promising, but also conflicting based on results in its efficacy for respiratory infections in childhood (Basnet, Mathisen, and Strand 2015; Singh and Das 2013).

No studies were found that directly compared medication and food. When we examined separate studies on drugs like zanamivir or oseltamivir (both antiviral medications), the reduction in duration of the illness was shown to be 1–2.5 days and 1.5 days, respectively (Makela et al. 2000; Matsumoto et al. 1999; Nicholson et al. 2000; Lavelle, Uyeki, and Prosser 2012). Ergoferon is an antiviral complex drug containing released-active forms of antibodies to interferon gamma, CD4 and histamine. It was investigated for efficacy compared to oseltamivir, and both were found to be equally effective in reducing the duration of flu-related symptoms (Rafalsky et al. 2016).

The studies on food products, supplements and drugs cannot be compared to each other because of a lack of uniformity in the populations studied and outcomes measured. However, some food products seem to show a diverse but favorable trend. This underscores the concept of food synergy, that the combination of all phytochemicals, micro- and macronutrients, is superior to the sum of each individual component (Jacobs, Gross, and Tapsell 2009; Jacobs and Tapsell 2007; Jacobs and Tapsell 2013). This is underlined by the supplement studies, since they do not show a clear positive effect. Different foods have different pathways by which they influence host immunity or the invasiveness of pathogens. In theory, they can also be used simultaneously, though this has not been investigated. One combination (probiotics, xylitol and vitamin C) of food products and the Mediterranean diet did show a significant positive effect, but there was no investigation of whether it is superior compared to one food group alone (Da Boit et al. 2015).

Other food products, such as synbiotics, honey and raw cow's milk, have also been investigated for recurrent URTIs, but are not included in our review, because none of the studies fitted our inclusion criteria (Sazawal et al. 2010; Schrezenmeir et al. 2004; Cohen et al. 2012; Paul et al. 2007; Loss et al. 2015).

Implications for clinical practice

We carried out the review on food products that are easily available, so, there is no barrier to using or obtaining the food products. The literature implicates that antiviral drugs or supplements are not clearly superior to food, and therefore, food can serve as a good alternative. The individual patient can buy food with health benefits without a prescription or having to visit a doctor.

Another aspect to be considered is health costs. A treatment with oseltamivir, for example, costs \$46–\$116 per treatment, depending on the age and weight of the patient (Lavelle, Uyeki, and Prosser 2012). The above amount is only the price of the medication, other costs like the number of outpatient visits, costs of other medications, emergency department visits or hospitalization were not considered. Also, the costs of adverse effects of oseltamivir (gastrointestinal or neuropsychiatric problems) or oseltamivir resistance were not considered. The prices of kiwifruit or elderberry are much lower and do not depend on health insurance policies.

Most studies were single studies, only a few food products are investigated in multiple studies, so implications for clinical practice cannot be made easily. However, the studies about probiotics, growing up milk and elderberries showed an overall low risk of bias and were investigated by several study groups. Especially probiotics and elderberry extract shows significant positive effects in several patient groups.

Methodological limitations of the studies reviewed

Because of a lack of uniformity, the studies could not be used for a meta-analysis or comparisons between the different food products. As with clinical intervention studies, there was some risk for bias (Table 4). Several studies used self-reported symptoms, which increases the risk of bias. Furthermore, small sample sizes could have resulted in a limited statistical power. Moreover, most of the food products were investigated in single studies. When there was more than one study, most of them were performed by the same research group.

Because of the diversity in study populations, the results are not generalizable. One food group can show distinct effects in different age or patient groups. This implicates that the benefits found in a specific study group may not be beneficial to everyone.

Comparison with other reviews

Until now, only (Cochrane) reviews have been published on food and URTIs concerning a single food product (Hao, Dong, and Wu 2015; Lissiman, Bhasale, and Cohen 2014; Azarpazhooh, Lawrence, and Shah 2016). This is the first study to review all whole food products studied and their effect on URTIs. Therefore, our study gives an overview and is an important addition to this field of research.

Conclusion

Food interventions are promising for reducing the incidence (growing-up milk, probiotics, prebiotics, fish oil, kiwi, garlic, Mediterranean diet and xylitol) and duration (elderberry, probiotics, kiwi, growing-up milk and fish oil) of respiratory infections or symptoms in selective patient groups. Still, the studies are diverse and have only been performed by a few study groups. When the risk of bias and repetition is taken into account, probiotics and elderberry show favorable effects. Food intervention studies are promising for reducing the incidence and duration of upper respiratory tract infections. However, further research is necessary to make clear and widespread conclusions.

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