*British Journal of Nutrition* (2013), **110**, 1188–1194
doi:10.1017/S0007114513001712




British Journal of Nutrition

*Systematic Review with Meta-analysis*

# Effect of probiotic fermented milk on blood pressure: a meta-analysis of randomised controlled trials

Jia-Yi Dong[1], Ignatius M. Y. Szeto[2], Kimmo Makinen[3], Qiutao Gao[2], Junkuan Wang[2], Li-Qiang Qin[1]* and Youyou Zhao[2]*

[1]*Department of Nutrition and Food Hygiene, School of Public Health, Soochow University, 199 Renai Road, Dushu Lake Higher Education Town, Suzhou 215123, People's Republic of China*
[2]*Nestlé Research Center Beijing, Building 5, No. 5 Dijin Road, Haidian District, Beijing 100095, People's Republic of China*
[3]*Nestlé Research Center, Lausanne, Switzerland*

*(Submitted 7 January 2013 – Final revision received 23 April 2013 – Accepted 25 April 2013 – First published online 3 July 2013)*

## Abstract

Previous studies have suggested that probiotic fermented milk may possess blood pressure (BP)-lowering properties. In the present study, we aimed to systematically examine the effect of probiotic fermented milk on BP by conducting a meta-analysis of randomised controlled trials. PubMed, Cochrane library and the ClinicalTrials.gov databases were searched up to March 2012 to identify eligible studies. The reference lists of the obtained articles were also reviewed. Either a fixed-effects or a random-effects model was used to calculate the combined treatment effect. Meta-analysis of fourteen randomised placebo-controlled trials involving 702 participants showed that probiotic fermented milk, compared with placebo, produced a significant reduction of 3·10 mmHg (95 % CI −4·64, −1·56) in systolic BP and 1·09 mmHg (95 % CI −2·11, −0·06) in diastolic BP. Subgroup analyses suggested a slightly greater effect on systolic BP in hypertensive participants than in normotensive ones (−3·98 *v.* −2·09 mmHg). Analysis of trials conducted in Japan showed a greater reduction than those conducted in European countries for both systolic BP (−6·12 *v.* −2·08 mmHg) and diastolic BP (−3·45 *v.* −0·52 mmHg). Some evidence of publication bias was present, but sensitivity analysis excluding small trials that reported extreme results only affected the pooled effect size minimally. In summary, the present meta-analysis suggested that probiotic fermented milk has BP-lowering effects in pre-hypertensive and hypertensive subjects.

**Key words: Probiotics: Fermented milk: Blood pressure: Meta-analyses: Randomised controlled trials**

Fermented milk, such as yogurt and cultured soured milk, has been considered as a functional food and widely consumed over the world for centuries. Fermented milk is a product obtained from the fermentation of milk by the action of suitable micro-organisms and the resultant reduction of pH with or without coagulation (isoelectric precipitation). The commonly used micro-organisms for the fermentation process include *Streptococcus thermophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus acidophilus* and *Lactobacillus kefiri*. Today, other micro-organisms are increasingly being used to produce fermented milk. Since this fermented milk has been shown to have a number of pleiotropic health benefits, it may be referred to as probiotic fermented milk[1]. Evidence from large prospective cohort studies has suggested that probiotic fermented milk may exert protective effects against many chronic diseases, including type 2 diabetes[2], CVD[3] and stroke[4]. Also, a recent meta-analysis of clinical trials has reported that consumption of probiotic yogurt significantly lowers total cholesterol and LDL-cholesterol concentrations[5]. However, a number of clinical trials investigating the effect of probiotic fermented milk on blood pressure (BP) have yielded mixed results[6–18]. These inconsistent findings may result from differences in sample size, study intervention, study population or study quality, and therefore a clear view on the overall impact of probiotic fermented milk on BP is difficult to obtain. Thus, in the present study, we aimed to systematically examine the effect of probiotic fermented milk on BP by conducting a meta-analysis of randomised controlled trials.

**Abbreviation:** BP, blood pressure.

***Corresponding authors:** L.-Q. Qin, email qinliqiang@suda.edu.cn; Y. Zhao, fax +86 10 5987 1301, email youyou.zhao@rd.nestle.com

British Journal of Nutrition

## Experimental methods

### Literature search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in the report of this meta-analysis[19]. We conducted an electronic search of PubMed, Cochrane library and the ClinicalTrials.gov databases up to March 2012 for relevant studies. Search terms included 'yogurt', 'yoghurt', 'sour milk', 'fermented milk', 'probiotic', 'blood pressure' and 'hypertension'. Reference lists in the retrieved articles obtained from the electronic search were also manually scanned.

### Study selection

Studies were included if they (1) were randomised, placebo-controlled trials, (2) used probiotic fermented milk as the intervention product and (3) reported the net changes in BP and the associated standard deviations (or data to calculate them). Because we aimed to examine the effect of probiotic fermented milk, studies using enzymatically hydrolysed milk as the intervention product were excluded. We also excluded studies that had a co-intervention of other supplementations or were duplicate reports from the same trial.

### Data extraction and quality assessment

The following characteristics of each study were recorded: first author's last name, publication year and country of origin; design details, including whether parallel or cross-over and open label, single blind or double blind; treatment duration; daily dose of probiotic fermented milk. Participant characteristics including age, sex, baseline BP and antihypertensive medication use were also recorded. If more than one time point for follow-up was reported, we used the data from the longest follow-up time period. Similarly, we used the data from the highest dose when there was more than one single dose for the intervention. One study included two independent strata (hypertensive and normotensive) and was subsequently treated as two trials[7].

Study quality was assessed in terms of randomisation, allocation concealment, blinding, description of withdrawals and availability of intention-to-treat analysis.

### Statistical analysis

In parallel trials, the net effect of probiotic fermented milk on BP was calculated as the difference in mean systolic BP and diastolic BP change between the intervention and control groups. In cross-over trials, the effect of probiotic fermented milk was calculated as the difference in BP between the intervention and control periods. Studies that did not report standard deviation values had these values imputed from standard errors, CI or $P$ values using a standard formula[20].

The between-study heterogeneity was tested using Cochran's $Q$ test at the $P<0{\cdot}10$ level of significance. The $I^2$ statistic, a quantitative measure of inconsistency across studies, was also calculated[21]. Either a fixed-effects or, in the presence of heterogeneity, a random-effects model was used to calculate the pooled effect size.

To explore the possible influences of study designs and participant characteristics on combined effect sizes, we further conducted pre-specified subgroup analyses stratified by hypertension status, study location and duration of intervention. To test the robustness of the results, we performed sensitivity analyses limited to parallel trials, double-blind trials and trials in which participants did not use antihypertensive medications. In addition, we repeated the analyses by omitting one trial in each turn to investigate the influence of a single trial on the overall effect estimate.

Potential publication bias was assessed using Begg's funnel plots and Egger's regression test at the $P<0{\cdot}10$ level of significance[22]. In case of publication bias, a non-parametric 'trim and fill' method was used to adjust for this bias[23]. Alternatively, we performed a sensitivity analysis in which smaller studies that reported more extreme effect sizes were excluded. All analyses were performed using STATA version 11.0 (StataCorp). $P$ values $<0{\cdot}05$ were considered statistically significant, except where otherwise specified.

## Results

### Literature search

Fig. 1 shows the flow of the literature search. An initial search of the three electronic databases identified 235 records, of which the majority were excluded based on title and abstract scan, leaving twenty-seven articles for full-text review. Of these articles, fourteen were excluded because they used enzymatically hydrolysed milk or other fermented milk products rather than probiotic fermented milk as the intervention product, had a co-intervention of other supplementations, measured acute effect only or were duplicate reports from the same trial (detailed reasons for the exclusion of these fourteen articles are given in Table S1, available online). Finally, thirteen articles (fourteen trials) were selected for the final analysis.

### Study characteristics

The characteristics of studies and participants for the fourteen trials are given in Table 1. The trials were published between 1996 and 2010. Of the fourteen trials, eight were conducted in European countries and the remaining in Japan. The sample size varied from 20 to 108, with a sum of 702 and a median of 40. The treatment was double blind in eleven trials, single blind in two trials and open label in the remaining one trial. All trials but one had a parallel design. The duration of intervention was from 4 to 24 weeks, with a median of 8 weeks. The dose of probiotic fermented milk varied from 100 to 450 g/d, and most of the control groups received a milk-based placebo product (e.g. artificially acidified milk). In eight trials, all participants were hypertensive patients; in three trials, patients used antihypertensive medications.

Study quality differed across the trials (Table SII, available online). All trials reported random allocation, but few of

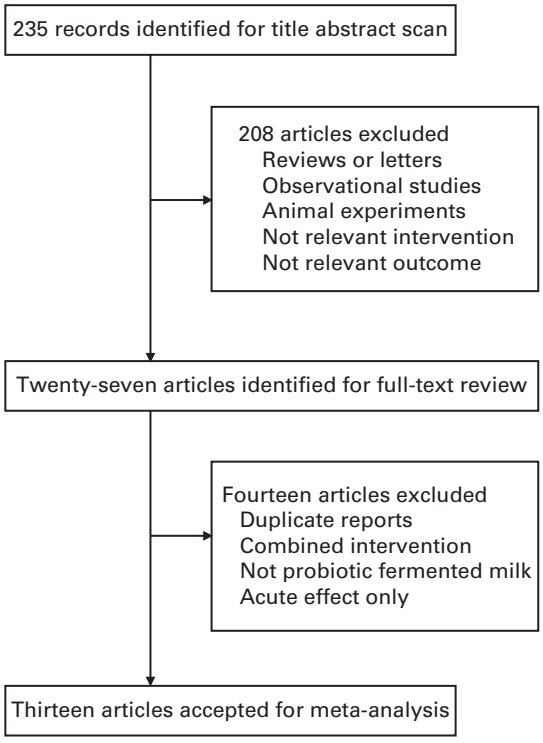


**Fig. 1.** Flow chart of the study selection.

them reported details of sequence generation and allocation concealment. In nine trials, dropout reasons along with numbers were mentioned. Another three trials analysed data according to an intention-to-treat principle.

### *Main analysis*

Of the fourteen trials, thirteen reported a reduction in systolic BP after probiotic fermented milk intervention, with mean net changes ranging from −1·5 to −12·4 mmHg. Compared with the control, the pooled effect size was −3·10 mmHg (95% CI −4·64, −1·56) for systolic BP (Fig. 2), with no evidence of heterogeneity between the trials ($P$=0·19 and $I^2$ = 24·1%).

Of the thirteen trials, one trial[7] reported data for systolic BP only and eleven trials reported a reduction in diastolic BP after probiotic fermented milk consumption, with mean net changes ranging from −0·3 to −6·5 mmHg. The pooled effect size was −1·09 mmHg (95% CI −2·11, −0·06) for diastolic BP (Fig. 3), without an indication of heterogeneity ($P$=0·15 and $I^2$ = 29%).

### *Subgroup and sensitivity analyses*

Table 2 presents the results of subgroup analyses according to hypertension status, study location and duration of intervention. Hypertensive participants, compared with normotensive ones, experienced a greater reduction in systolic BP (−3·98 *v.* −2·09 mmHg). Trials conducted in Japan, compared with those carried out in European countries, showed a markedly greater reduction in both systolic BP (−6·12 *v.* −2·08 mmHg) and diastolic BP (−3·45 *v.* −0·52 mmHg).

Table 3 presents the results of sensitivity analyses limited to parallel trials, double-blind trials and trials excluding participants using antihypertensive medications. In general, the results were similar with the overall combined effect sizes. Repeated analyses examining the impact of a single trial on the overall results by omitting one trial in each turn yielded a range from −3·64 mmHg (95% CI −5·25, −2·03) to −2·68 mmHg (95% CI −4·26, −1·11) for systolic BP and from −0·90 mmHg (95% CI −1·95, 0·15) to −1·64 mmHg (95% CI −2·76, −0·47) for diastolic BP.

### *Publication bias*

Visual inspection of Begg's funnel plots showed some asymmetry, and Egger's test suggested evidence of publication bias ($P$=0·02 for systolic BP and $P$=0·002 for diastolic BP). However, in a sensitivity analysis using a non-parametric 'trim and fill' method, no study was removed and the overall effect size remained unchanged. When small trials showing more extreme results were excluded[6,9,13], the pooled effect size was slightly attenuated to −2·26 mmHg (95% CI −3·88, −0·64) for systolic BP and −0·69 mmHg (95% CI −1·76,

**Table 1.** Characteristics of clinical trials examining the effect of probiotic fermented milk on blood pressure (BP)

| Study | Location | Design | Duration (weeks) | Dose (ml/d) | Age | Sex (M/F) | Baseline BP (mmHg) | Antihypertensive drug use |
|---|---|---|---|---|---|---|---|---|
| Hata (1996)[6] | Japan | R, PC, P | 8 | 100 | 75 | 8/22 | 159/89 *v.* 151/87 | Yes |
| Agerholm-Larsen (2000)[7] | Denmark | R, PC, DB, P | 8 | 450 | 39 | 9/21 | 121/79 *v.* 117/76 | No |
| Kawase (2000)[8] | Japan | R, PC, SB, P | 8 | 400 | 40·1 | 20/0 | 124/– *v.* 124/– | No |
| Inoue (2003)[9] | Japan | R, PC, SB, P | 12 | 100 | 55 | 20/15 | 155/93 *v.* 150/93 | No |
| Seppo (2003)[10] | Finland | R, PC, DB, P | 21 | 150 | 49·6 | 19/20 | 155/97 *v.* 152/96 | Yes |
| Mizushima (2004)[11] | Japan | R, PC, DB, P | 4 | 160 | 46·4 | 46/0 | 148/93 *v.* 145/92 | No |
| Tuomilehto (2004)[12] | Finland | R, PC, DB, P | 10 | 150 | 52·7 | 36/24 | 153/98 *v.* 157/98 | No |
| Aihara (2005)[13] | Japan | R, PC, DB, P | 4 | 150 | 51·5 | 26/14 | 137/85 *v.* 137/85 | No |
| Aihara (2005)[13] | Japan | R, PC, DB, P | 4 | 150 | 51·5 | 32/8 | 147/92 *v.* 149/93 | No |
| Jauhiainen (2005)[14] | Finland | R, PC, DB, P | 10 | 300 | 53 | 36/72 | 149/94 *v.* 150/93 | No |
| Engberink (2008)[15] | The Netherlands | R, PC, DB, P | 8 | 200 | 58·8 | 43/24 | 142/83 *v.* 141/84 | Yes |
| van der Zander (2008)[16] | The Netherlands | R, PC, DB, X | 4 | 250 | 35–70 | 42 | 130/81 *v.* 128/81 | No |
| Jauhiainen (2010)[17] | Finland | R, PC, DB, P | 24 | 400 | 49 | 54/35 | 155/94 *v.* 151/95 | No |
| Usinger (2010)[18] | Denmark | R, PC, DB, P | 8 | 300 | 55 | 29/30 | 134/95 *v.* 134/94 | No |

M, male; F, female; R, randomised; PC, placebo controlled; P, parallel; DB, double blind; SB, single blind; –, no information available; X, cross-over.

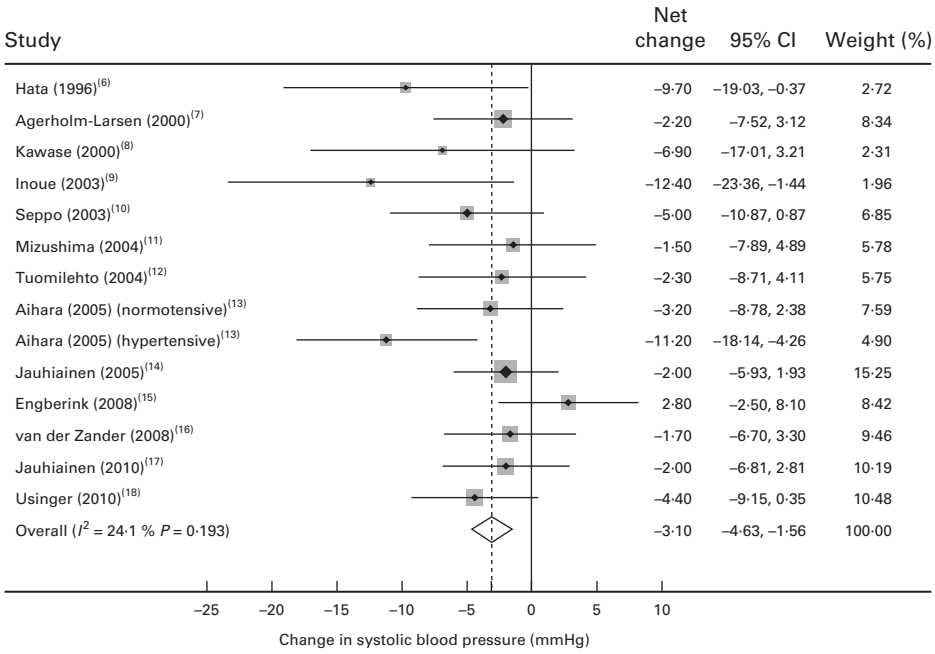


**Fig. 2.** Meta-analysis of the effect of probiotic fermented milk on systolic blood pressure when compared with placebo.

0·39) for diastolic BP. As indicated by Egger's test, publication bias disappeared for systolic BP ($P$=0·39), but it may remain for diastolic BP ($P$=0·06).

## Discussion

The present meta-analysis systematically examined the effect of probiotic fermented milk on BP. Findings from the present study showed that probiotic fermented milk, compared with placebo, produced a significant reduction of 3 mmHg in systolic BP and 1 mmHg in diastolic BP. The magnitudes of BP reductions reported herein are modest. However, on a population level, even a small reduction in BP could have important public health consequences; a 2 mmHg decrease in systolic BP has been shown to be associated with 10 % lower stroke mortality and 7 % lower CHD mortality[24].

We observed that probiotic fermented milk had a slightly greater effect on systolic BP in hypertensive participants than in normotensive ones (−3·98 *v.* −2·09 mmHg). This highlights the potential role of probiotic fermented milk in the control and treatment of hypertension. The Dietary Approaches to Stop Hypertension trial demonstrated that a dietary pattern abundant in fruits, vegetables and low-fat dairy products can considerably reduce BP[25]. Data from

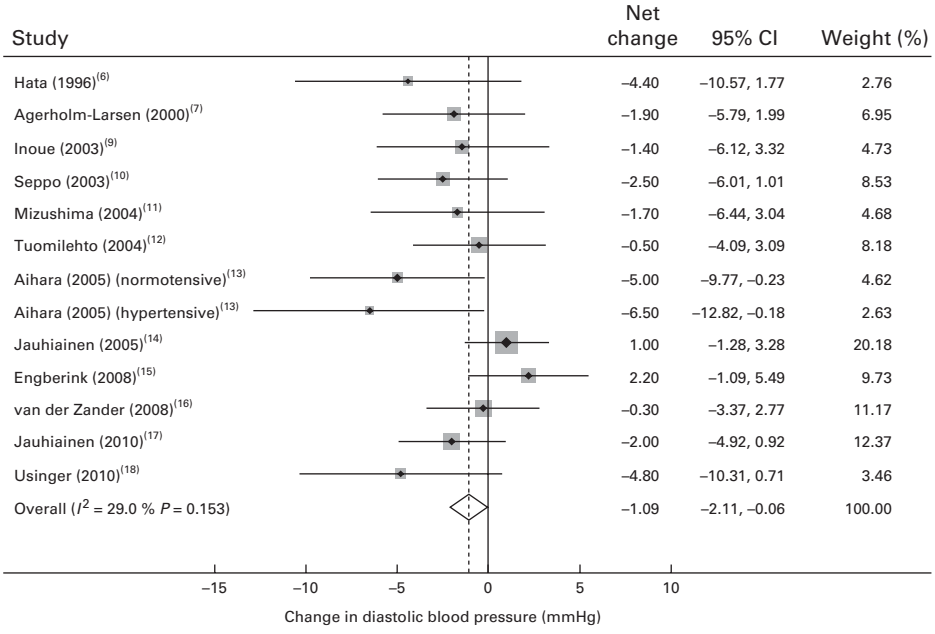


**Fig. 3.** Meta-analysis of the effect of probiotic fermented milk on diastolic blood pressure when compared with placebo.

**Table 2.** Subgroup analyses according to hypertension status, study location and duration of intervention

| | Systolic blood pressure (mmHg) | | | | | Diastolic blood pressure (mmHg) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Groups | Trials (*n*) | Net change | 95 % CI | $P_{heterogeneity}$ | $I^2$ (%) | Trials (*n*) | Net change | 95 % CI | $P_{heterogeneity}$ | $I^2$ (%) |
| Total | 14 | −3·10 | −4·64, −1·56 | 0·19 | 24·1 | 13 | −1·09 | −2·11, −0·06 | 0·15 | 29 |
| Hypertension | | | | | | | | | | |
| Yes | 8 | −3·98 | −6·08, −1·88 | 0·17 | 33 | 8 | −1·15 | −2·43, 0·13 | 0·31 | 15·8 |
| No | 6 | −2·09 | −4·34, 0·17 | 0·39 | 4·4 | 5 | −1·45 | −4·04, 1·14 | 0·07 | 53·3 |
| Location | | | | | | | | | | |
| Europe | 8 | −2·08 | −3·86, −0·30 | 0·64 | 0 | 8 | −0·52 | −1·66, 0·62 | 0·23 | 25·2 |
| Japan | 6 | −6·12 | −9·17, −3·06 | 0·22 | 28·2 | 5 | −3·45 | −5·77, −1·12 | 0·62 | 0 |
| Duration | | | | | | | | | | |
| ≤ 8 weeks | 9 | −3·43 | −6·07, −0·79 | 0·1 | 40·3 | 8 | −2·09 | −4·17, −0·01 | 0·1 | 42·6 |
| > 8 weeks | 5 | −3·07 | −5·50, −0·64 | 0·44 | 0 | 5 | −0·68 | −2·07, 0·72 | 0·41 | 0 |

the present study provide further support for an important role of probiotic fermented milk in the Dietary Approaches to Stop Hypertension diet. Also, a recent finding based on the Framingham Heart Study Offspring Cohort has demonstrated that normotensive adults who had a high intake of yogurt (>2% of total daily energy intake) were 31% less likely to develop incident hypertension over 15 years[26].

Another interesting finding of the present meta-analysis was that study location (Japan *v.* European countries) may modify the effect of probiotic fermented milk on BP. Analysis of trials conducted in Japan showed a greater reduction than those conducted in European countries for both systolic BP (−6·12 *v.* −2·08 mmHg) and diastolic BP (−3·45 *v.* −0·52 mmHg). The average intake of dairy foods in the Japanese population is lower than that in Western populations, and hence the intervention markedly enhanced their milk intake, especially fermented milk intake, which might explain the pronounced hypotensive effect observed in Japanese trials[27]. Alternatively, the weaker methodology used in some Japanese trials (e.g. insufficient blinding) might have overestimated the true effect of the treatment. A similar observation was also made for the BP-lowering effect of lactotripeptide consumption among Japanese, Finland and Netherlandish studies[28], and ethnic difference in genetic disposition has been suggested to contribute to various degrees of hypertension[29]. However, due to a limited number of trials being performed to date, it is still inconclusive to confirm the role of genotype polymorphism in the underlying BP-lowering mechanism in the present study.

Several functional components in probiotic fermented milk may account for the BP-lowering effects. It is also possible that different fermented milk products act via different mechanisms or that a single product acts via multiple mechanisms. Two tripeptides, valine–proline–proline and isoleucine–proline–proline, have been extensively studied[30], and, indeed, many products used in the trials included in the present meta-analysis contained them. These tripeptides exert angiotensin-converting enzyme inhibitory activity *in vitro* and are hypothesised to lower BP through this mechanism[31]. In fact, two recent meta-analyses of clinical trials have documented mild BP-lowering effects of valine–proline–proline and isoleucine–proline–proline interventions[30,32], although the summary effect sizes were relatively weaker in the latter one[32]. The fermented product used in the study carried out by Inoue *et al.*[9], however, exhibited no angiotensin-converting enzyme-inhibiting activity. Instead, the authors attributed the BP-lowering effect to the presence of γ-aminobutyric acid, where the test product contained 10–12 mg/ml, which has been shown to lower BP when administered orally to human subjects[33].

Probiotic micro-organisms found in fermented milk, such as *Lactobacillus helveticus* and *L. acidophilus*, may influence gut microbiota composition, which is suggested to have an impact on the development of metabolic disorders[34]. It has also been suggested that bacterial cell wall fragments may have an antihypertensive effect[35,36]. Indeed, studies examined in the present meta-analysis used live micro-organisms in addition to the fermented base and, thus, the effect could have been at least partially attributable to them. However, in the Aihara *et al.*[13] study, the test product displayed BP-lowering effects despite being depleted of bacterial fragments. In addition, no studies on the effect of pure probiotic biomass on BP in human subjects have been published. One study has investigated the effect of fermented rosehip drink

**Table 3.** Sensitivity analyses restricted to certain trials

| | Systolic blood pressure (mmHg) | | | | | Diastolic blood pressure (mmHg) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Restriction | Trials (*n*) | Net change | 95 % CI | $P_{heterogeneity}$ | $I^2$ (%) | Trials (*n*) | Net change | 95 % CI | $P_{heterogeneity}$ | $I^2$ (%) |
| Parallel | 13 | −3·24 | −4·86, −1·63 | 0·16 | 28·6 | 12 | −1·19 | −2·27, −0·10 | 0·12 | 33·8 |
| Double-blinding | 11 | −2·62 | −4·21, −1·02 | 0·32 | 13·4 | 11 | −0·97 | −2·04, 0·09 | 0·11 | 36·4 |
| No use of antihypertensive drugs | 11 | −3·33 | −5·02, −1·63 | 0·44 | 0 | 10 | −1·22 | −2·38, −0·07 | 0·26 | 20·2 |



British Journal of Nutrition

on BP, but this product, similar to fermented milk, comprised the fermented matrix and the fermenting micro-organisms, both with potential functional contributions[37]. Finally, some of the BP-lowering effects of fermented milk may derive from the mineral content of milk products, including K, Ca and P, proposed to exhibit an antihypertensive activity[38]. However, the observed BP-lowering effects were probably not due to these minerals, because they were well balanced between the intervention and control groups in most trials.

To date, several prospective cohort studies have examined the association between fermented milk (mainly yogurt) consumption and the risk of developing hypertension[39–42]. All these studies have shown an inverse relationship with the relative risk, which ranged from 0·85 to 0·97, but none of them reached statistical significance. We hence combined these data and obtained a summary relative risk of 0·91 (95% CI 0·84, 1·00; $P=0·04$), indicating that higher intake of yogurt, compared with lower intake, was associated with a 9% reduced risk of developing hypertension. Therefore, the findings of the present meta-analysis of randomised controlled trials are in line with those from cohort studies, both supporting a hypotensive effect of fermented milk.

The major strength of the present study is that all the included trials had a randomised, placebo-controlled design. Such a design minimises the risk of confounding bias, which is of great concern in observational studies. In addition, using a meta-analysis approach, we enlarged the sample size and hence increased the statistical power. However, potential limitations involved in either primary studies or the present meta-analysis should be considered while interpreting the findings. First, we included only published studies in the meta-analysis, raising the risk of publication bias. Funnel plots for both systolic BP and diastolic BP showed evidence of possible bias, favouring the publication of small trials with extreme effects. However, these trials had small weights in the present meta-analysis and excluding them from the analysis led to only a slight attenuation of the effect on systolic BP. Second, as with any meta-analysis, the validity depended upon the quality of primary studies. Although all trials were randomised and placebo controlled, the study quality varied; for example, the lack of double-blinding in several trials increased the risk of expectation bias[6,8,9]. Nevertheless, sensitivity analyses limited to double-blind trials yielded similar results. Third, most trials had a relatively small sample size ($n<60$) and short treatment duration (<3 months). As has been mentioned previously, small studies with more extreme results may have increased the risk of publication bias, posing a potential threat to the validity of the present meta-analysis. Because of the short duration, whether the findings could translate into a long-term treatment effect is uncertain.

## Conclusion

In summary, the present meta-analysis suggested that probiotic fermented milk has BP-lowering effects in pre-hypertensive and hypertensive subjects. However, while the role of fermented milk bioactives in BP lowering is well studied, the potential contribution to BP lowering by live micro-organisms exerting a probiotic effect remains to be elucidated in human subjects. Consequently, for the time being, the term 'probiotic', defined as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host', is best avoided in connection with BP-lowering fermented milk. Well-designed, large-scale trials are required to confirm these findings.

## Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114513001712

## Acknowledgements

The present study was funded by Nestec Limited (Nestlé R&D (China) Limited). L.-Q. Q. and Y. Z. designed the research. J.-Y. D. and L.-Q. Q. conducted the research. J.-Y. D. analysed the data. All authors wrote the paper. L.-Q. Q. and Y. Z. had the primary responsibility for the final content. None of the authors has any conflicts of interest with respect to the present study.

## References

1. Ebringer L, Ferencík M & Krajcovic J (2008) Beneficial health effects of milk and fermented dairy products – review. *Folia Microbiol (Praha)* **53**, 378–394.
2. Tong X, Dong JY, Wu ZW, *et al.* (2011) Dairy consumption and risk of type 2 diabetes mellitus: a meta-analysis of cohort studies. *Eur J Clin Nutr* **65**, 1027–1031.
3. Sonestedt E, Wirfalt E, Wallstrom P, *et al.* (2011) Dairy products and its association with incidence of cardiovascular disease: the Malmo diet and cancer cohort. *Eur J Epidemiol* **26**, 609–618.
4. Dalmeijer GW, Struijk EA, van der Schouw YT, *et al.* (2012) Dairy intake and coronary heart disease or stroke – a population-based cohort study. *Int J Cardiol* (Epublication ahead of print version 4 April 2012).
5. Guo Z, Liu XM, Zhang QX, *et al.* (2011) Influence of consumption of probiotics on the plasma lipid profile: a meta-analysis of randomised controlled trials. *Nutr Metab Cardiovasc Dis* **21**, 844–850.
6. Hata Y, Yamamoto M, Ohni M, *et al.* (1996) A placebo-controlled study of the effect of sour milk on blood pressure in hypertensive subjects. *Am J Clin Nutr* **64**, 767–771.
7. Agerholm-Larsen L, Raben A, Haulrik N, *et al.* (2000) Effect of 8 week intake of probiotic milk products on risk factors for cardiovascular diseases. *Eur J Clin Nutr* **54**, 288–297.
8. Kawase M, Hashimoto H, Hosoda M, *et al.* (2000) Effect of administration of fermented milk containing whey protein concentrate to rats and healthy men on serum lipids and blood pressure. *J Dairy Sci* **83**, 255–263.
9. Inoue K, Shirai T, Ochiai H, *et al.* (2003) Blood-pressure-lowering effect of a novel fermented milk containing gamma-aminobutyric acid (GABA) in mild hypertensives. *Eur J Clin Nutr* **57**, 490–495.
10. Seppo L, Jauhiainen T, Poussa T, *et al.* (2003) A fermented milk high in bioactive peptides has a blood pressure-lowering effect in hypertensive subjects. *Am J Clin Nutr* **77**, 326–330.

11. Mizushima S, Ohshige K, Watanabe J, *et al.* (2004) Randomized controlled trial of sour milk on blood pressure in borderline hypertensive men. *Am J Hypertens* **17**, 701–706.
12. Tuomilehto J, Lindstrom J, Hyyrynen J, *et al.* (2004) Effect of ingesting sour milk fermented using *Lactobacillus helveticus* bacteria producing tripeptides on blood pressure in subjects with mild hypertension. *J Hum Hypertens* **18**, 795–802.
13. Aihara K, Kajimoto O, Hirata H, *et al.* (2005) Effect of powdered fermented milk with *Lactobacillus helveticus* on subjects with high-normal blood pressure or mild hypertension. *J Am Coll Nutr* **24**, 257–265.
14. Jauhiainen T, Vapaatalo H, Poussa T, *et al.* (2005) *Lactobacillus helveticus* fermented milk lowers blood pressure in hypertensive subjects in 24-h ambulatory blood pressure measurement. *Am J Hypertens* **18**, 1600–1605.
15. Engberink MF, Schouten EG, Kok FJ, *et al.* (2008) Lactotripeptides show no effect on human blood pressure: results from a double-blind randomized controlled trial. *Hypertension* **51**, 399–405.
16. van der Zander K, Jakel M, Bianco V, *et al.* (2008) Fermented lactotripeptides-containing milk lowers daytime blood pressure in high normal-to-mild hypertensive subjects. *J Hum Hypertens* **22**, 804–806.
17. Jauhiainen T, Ronnback M, Vapaatalo H, *et al.* (2010) Long-term intervention with *Lactobacillus helveticus* fermented milk reduces augmentation index in hypertensive subjects. *Eur J Clin Nutr* **64**, 424–431.
18. Usinger L, Ibsen H, Linneberg A, *et al.* (2010) Human *in vivo* study of the renin–angiotensin–aldosterone system and the sympathetic activity after 8 weeks daily intake of fermented milk. *Clin Physiol Funct Imaging* **30**, 162–168.
19. Moher D, Liberati A, Tetzlaff J, *et al.* (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* **151**, 264–269.
20. Higgins J & Green S (2011) *Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0*. The Cochrane Collaboration. http://www.cochrane-handbook.org (accessed 9 March 2012).
21. Higgins JP & Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* **21**, 1539–1558.
22. Egger M, Davey Smith G, Schneider M, *et al.* (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634.
23. Duval S & Tweedie R (2000) Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* **56**, 455–463.
24. Lewington S, Clarke R, Qizilbash N, *et al.* (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* **360**, 1903–1913.
25. Appel LJ, Moore TJ, Obarzanek E, *et al.* (1997) A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* **336**, 1117–1124.
26. Wang H, Livingstone KA, Mayer J, *et al.* (2012) Yogurt consumption, blood pressure and incident hypertension: a longitudinal study in the Framingham Heart Study. Presented at the American Heart Association High Blood Pressure Research Scientific Sessions, 21 September 2012, Washington, DC (Abstract 188).
27. Usinger L, Ibsen H & Jensen LT (2009) Does fermented milk possess antihypertensive effect in humans? *J Hypertens* **27**, 1115–1120.
28. Qin LQ, Xu JY, Dong JY, *et al.* (2013) Lactotripeptides intake and blood pressure management: a meta-analysis of randomised controlled clinical trials. *Nutr Metab Cardiovasc Dis* **23**, 395–402.
29. Kato N (2012) Ethnic differences in genetic predisposition to hypertension. *Hypertens Res* **35**, 574–581.
30. Xu JY, Qin LQ, Wang PY, *et al.* (2008) Effect of milk tripeptides on blood pressure: a meta-analysis of randomized controlled trials. *Nutrition* **24**, 933–940.
31. Ricci I, Artacho R & Olalla M (2010) Milk protein peptides with angiotensin I-converting enzyme inhibitory (ACEI) activity. *Crit Rev Food Sci Nutr* **50**, 390–402.
32. Cicero AF, Gerocarni B, Laghi L, *et al.* (2011) Blood pressure lowering effect of lactotripeptides assumed as functional foods: a meta-analysis of current available clinical trials. *J Hum Hypertens* **25**, 425–436.
33. Research Group of γ-Aminobutyric Acid in Tokyo (1960) Clinical aspects on the use of gamma-aminobutyric acid. In *Inhibition in the Nervous System and Gamma-aminobutyric Acid. Proceedings of an International Symposium*, 22–24 May 1959, City of Hope Medical Center, Duarte, CA, pp. 579–581. Oxford: Pergamon Press.
34. Cani PD & Delzenne NM (2009) The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des* **15**, 1546–1558.
35. Sawada H, Furushiro M, Hirai K, *et al.* (1990) Purification and characterization of an antihypertensive compound from *Lactobacillus casei*. *Agric Biol Chem* **54**, 3211–3219.
36. Nakajima K, Hata Y, Osono Y, *et al.* (1995) Antihypertensive effect of extract of *Lactobacillus casei* in patients with hypertension. *J Clin Biochem Nutr* **18**, 181–187.
37. Naruszewicz M, Johansson ML, Zapolska-Downar D, *et al.* (2002) Effect of *Lactobacillus plantarum* 299v on cardiovascular disease risk factors in smokers. *Am J Clin Nutr* **76**, 1249–1255.
38. McGrane MM, Essery E, Obbagy J, *et al.* (2011) Dairy consumption, blood pressure, and risk of hypertension: an evidence-based review of recent literature. *Curr Cardiovasc Risk Rep* **5**, 287–298.
39. Steffen LM, Kroenke CH, Yu X, *et al.* (2005) Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr* **82**, 1169–1177.
40. Wang L, Manson JE, Buring JE, *et al.* (2008) Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension* **51**, 1073–1079.
41. Engberink MF, Geleijnse JM, de Jong N, *et al.* (2009) Dairy intake, blood pressure, and incident hypertension in a general Dutch population. *J Nutr* **139**, 582–587.
42. Engberink MF, Hendriksen MA, Schouten EG, *et al.* (2009) Inverse association between dairy intake and hypertension: the Rotterdam Study. *Am J Clin Nutr* **89**, 1877–1883.


British Journal of Nutrition