Original Article

Habitual dietary calcium intakes and calcium metabolism in healthy adults Chinese: a systematic review and meta-analysis

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To investigate the metabolic differences of calcium requirements between Chinese and Westerners, we examined systematically the characteristics of calcium metabolism in Chinese adults with habitual dietary calcium intakes. We searched PubMed, Cochrane Library, SinoMed, and National Index to Chinese Newspapers & Periodicals, from inception to March 17, 2015, as well as the bibliographies of any relevant papers and journals, for trials assessing calcium metabolism in healthy Chinese adults within 18-60 years of age on the typical Chinese diet. We extracted a standardized dataset from metabolic studies that reported intake, retention, urinary excretion, faecal excretion and/or fractional absorption of calcium. We pooled data with a random effects meta-analysis. Of 2,046 citations identified by the search strategy, 12 studies (comprising 137 participants, 13 aggregate data deriving from 257 individual data) met the inclusion criteria. Metabolic data with self-chosen or typical Chinese diets were analyzed. Mean daily intakes of calcium ranged between 288 and 948 mg. Mean calcium retentions of each study were between 13 and 294 mg/d. The overall pooled value for dietary intake, urinary excretion, faecal excretion, retention and fractional absorption of calcium were 583 mg/d, 117 mg/d, 381 mg/d, 72 mg/d and 33.3%. Dietary calcium intake and faecal calcium excretion explained almost 85% of the heterogeneity of calcium retention. Chinese adults could maintain a positive calcium balance with plant-based diets at calcium intakes as low as 300 mg/d through increasing fractional calcium absorption and decreasing calcium excretion in urine and faeces.

Key Words: calcium metabolism, Chinese adults, plant-based diets, meta-analysis, systematic review

INTRODUCTION

China is a country with a history of agricultural civilization for thousands of years. The typical plant-based dietary patterns consumed by Chinese,[1-3] have low calcium quantity and bioavailability. As the main source of dietary calcium, vegetables, legumes and cereals account for over 70 percent of the total daily calcium intakes.[4] Findings from nutrition surveys have shown that dietary calcium deficiency in Chinese, whose average calcium intake is about 400 mg/d, has been a major nutritional problem over the past few decades.[4-9] In terms of dietary calcium deficiency, we refer mostly to the intakes under the recommended allowances for calcium rather than physiological requirements.[10,11] While consuming habitual low calcium diets, Chinese show no sign of deceleration of the population growth. In the view of evolution, the body has to adapt itself to the transition of food supply to maintain the individual survival and race continuation. In our previous paper,[12] we reported a calcium requirement of 400-500 mg/d for Chinese adults between 18 and 60 years of age, which is much lower than that for Americans and Europeans.[13,14] It is wondered, therefore, if the faculty of adaptation to poor calcium intakes is a part of the physiological regulation of calcium metabolism in Chinese.

Metabolic studies over the past century may have revealed the characteristics of calcium metabolism in Chinese adults. Most of them focus on traditional Chinese diets, which allows us to explore whether Chinese were in an unfavourable position with calcium-deficiency, or whether physiological adaptation could compensate for low dietary calcium intakes in evolution. In the current review, we collected and pooled the metabolic studies among healthy Chinese adults with habitual low dietary calcium intakes, to investigate the metabolic differences between Chinese and Westerners.

MATERIALS AND METHODS

This systematic review and meta-analysis was reported in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and meta-Analyses) guidelines.

Search strategy

We searched PubMed, Cochrane Library, SinoMed, and National Index to Chinese Newspapers & Periodicals, from inception to March 17, 2015, for metabolic studies

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assessing calcium metabolism in Chinese adults. The search strategy used for searching PubMed was in the following format: (((((((("Calcium, Dietary" [Mesh] OR "dietary calcium" [All Fields]) OR "calcium intake" [All Fields]) AND (((("faecal calcium" [All Fields] OR "fecal calcium" [All Fields]) AND "urinary calcium" [All Fields]) OR "calcium excretion" [All Fields])) OR "calcium retention" [All Fields]) OR "calcium balance" [All Fields] AND "humans" [MeSH Terms]))) AND ((Chinese) OR China)). Similar strategy was used for searching the Cochrane Library, SinoMed and National Index to Chinese Newspapers & Periodicals were searched with the terms "calcium balance", or "calcium retention", or "calcium metabolism", or "calcium utilization", or "calcium bioavailability", or "calcium absorption", or "calcium requirement". The bibliographies of selected papers and journals were also screened for potentially eligible studies.

Selection criteria

To qualify for inclusion, metabolic studies had to be conducted among apparently healthy Chinese adults aged between 18 and 60 years, who consumed the typical Chinese diet without other interventions (e.g. calcium and/or vitamin D supplementation, activity restriction). Intake, retention, urinary excretion, faecal excretion and/or fractional absorption of calcium, as well as the relevant information of the studies (e.g. subject characteristics, study design, experimental diets), were given in detail. We excluded duplicates between the databases, review literatures, and studies in pregnant women, lactating women and postmenopausal women. More details about the number of studies assessed and included in the review are shown in Figure 1.

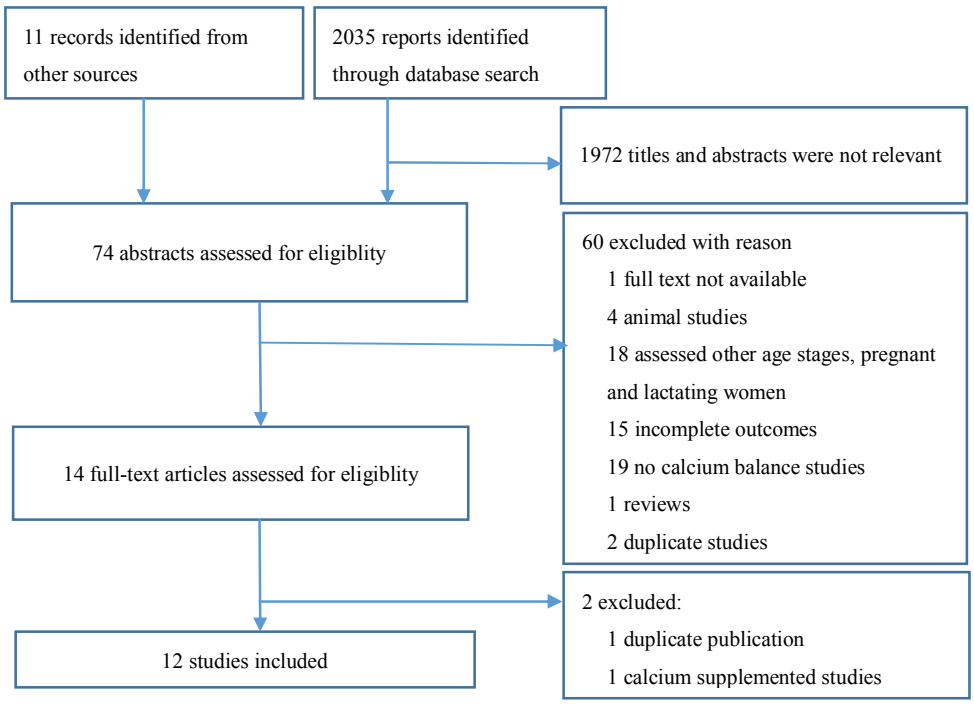
Data extraction and missing values

We extracted a standardized dataset from metabolic studies eligible, including general study information (e.g. first author, year for publication, region), study design (e.g. sample size, experimental diet, study period), subject characteristics (e.g. gender, age), and metabolic data (e.g. dietary intake, urinary excretion, faecal excretion, fractional absorption and retention of calcium). We excluded diet arms and data from subjects that did not meet the inclusion criteria from the analysis. Several of the individual studies used a sequential design where multiple diets were studied and multiple data points were collected in the same subjects. In order that each of them contributed only one data point to each meta-analysis, we first summarized the results from each of these sequential design studies. All the metabolic data were converted to mg/d and expressed as means (±standard errors (SEs)) where required. If means (±SEs) were not reported, the values were calculated from the individual participant data when available, otherwise missing standard deviations (SDs) were replaced by using simple imputation that borrowed SDs from other studies in the same meta-analysis,[15] and missing means were defined as follows:

Retention = Dietary intake - (Urinary excretion + Faecal excretion)

Fractional absorption (%) = [(Dietary intake - Faecal excretion) / Dietary intake] × 100 %

Two reviewers (FAP and LKJ) confirmed the eligibility of studies in parallel. All data from the qualifying studies were collated and extracted by FAP and were double checked by LKJ. Any discrepancy was settled through discussion.



1. Boxes: every step of study selecion.
2. Arrows: the direction of study selection.
3. Numbers in boxes: study numbers left after each step of study selection.

Figure 1. Flow chart of study selection

Statistical analyses

In calculation of summary estimates, all the included individual studies were assigned in four subsets based on the quartiles of mean daily dietary calcium intake. We pooled metabolic data with a random effect meta-analysis with original mean values and 95% CI reported. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using Cochran's Q statistic and the I^2 statistic. Additionally, to explore potential heterogeneity of calcium retention and estimate the effect of study characteristics (e.g. study design, year for publication, sample size, gender, age, study duration, and experimental diet) on calcium retention, we performed univariate and multivariate meta-regression analysis. The intake level associated with a zero balance was also estimated by using the univariate meta-regression of balance by intake. Potential publication bias was assessed with the Egger's test and represented graphically with Begg's funnel plots of calcium retention versus its standard error. A two-sided p value less than 0·05 was regarded as significant for all analyses. All statistical analyses were done with the STATA statistical software package (version 11.0 SE; Stata Corp).

RESULTS

Literature search

2, 046 articles were yielded by the literature search, 68 were reviewed in full text and 12 calcium metabolic studies met the inclusion criteria (Figure 1). These trials included a total of 137 subjects, among which 257 individual calcium metabolic data were reported (Some studies had multiple diet arms and the subjects were studied more than once), and expressed in 13 aggregate calcium metabolic data.

Study characteristics

Table 1 summarizes the characteristics of the included studies. The sample size ranged from 3 to 60 subjects. 10 studies included had more than one diet arm and were undertaken in both northern China and southern China. The studies assessing calcium metabolism were done between 1,932 and 2,007. The age of the study subjects ranged between 18 and 60 years, and 8 of them were done among younger adults (less than 30 years). Six studies enrolled only men, and one studies enrolled only women. The lengths of the studies ranged between 2 and 12 days, with 0-4 days of adaptation. All subjects consumed experimental diets. Foodstuffs used in each study were in general characteristics of typical Chinese diets.

Main analysis

As shown in Figure 2, mean calcium retentions of each arm fell in a wide range between 13 and 294 mg/d. All of them were on the right side of zero, that is, positive balance. Similarly, the variation of calcium retentions within studies was also large, which represented the individual differences.

Mean daily dietary intakes of calcium ranged between 288 and 948 mg. Subgroup analysis showed that average calcium retentions in four quartile groups were 45 mg/d, 18 mg/d, 85 mg/d and 163 mg/d, respectively.

There was significant heterogeneity within each subgroup except for the 2nd quartile. In univariate meta-regression (Table 2), dietary calcium intake explained 61.5% of the heterogeneity (p=0.006), followed by faecal calcium excretion (p=0.110). Urinary calcium excretion and fractional calcium absorption explained little of the heterogeneity (p=0.829 and p=0.517, respectively). A zero balance was reached at an intake of 274 mg/d based on the meta-regression model of balance by intake (Table 2). None of the study characteristics (e.g. study design, year for publication, sample size, gender, age, study duration, diet) was significantly associated with the heterogeneity of calcium retention.

The relationships between dietary intake, urinary excretion, faecal excretion, retention and fractional absorption for calcium were summarized in Table 3. The average dietary intakes for calcium in four quartile groups are 392 mg/d, 475 mg/d, 649 mg/d and 915 mg/d, respectively. The pooled urinary excretion for calcium ranged between 79 and 169 mg/d, with no evidence of increase with dietary calcium intakes. Faecal calcium excretion showed an increasing trend with dietary calcium intakes, fluctuating from 266 to 658 mg/d. Even though a rise in faecal calcium excretion was noted, there was a substantial increase in calcium retention. It may be noted in general that fractional calcium absorption was at a relatively high level of more than 30% in all but the highest quartile. The overall summary value for calcium intakes and retention were 583 mg/d and 72 mg/d.

Publication bias

Formal statistical testing showed no evidence of publication bias for the outcome of calcium retention (Begg's test p=0.111 and Egger's test p=0.933).

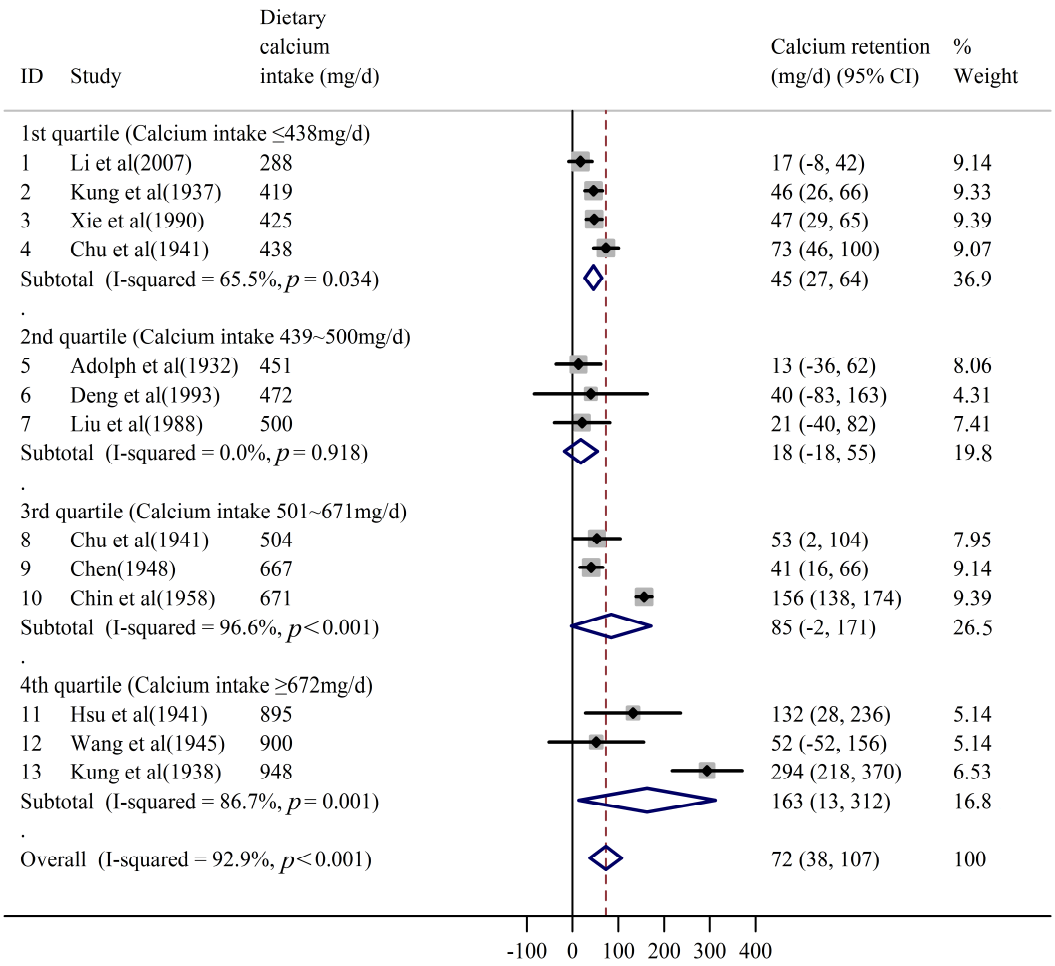
DISCUSSION

This quantitative review included 137 individuals in 12 studies with a wide variation in dietary calcium intakes, and 8 of the 12 included studies were published before 1960. Differences among the present studies were mainly in calcium assay and experimental diets rather than in study design. Compared to atomic absorption spectrophotometry commonly used today, chemical quantitative assay used in the past has lower sensitivity, equivalent accuracy and higher precision in general understanding. The experimental diets consumed in the studies before 1960 may be different from the later studies. Whereas the dietary calcium consumed by most Chinese adults is still around 400 mg/d, and the traditional plant-based calcium sources and the habitual low calcium content in diets have no evidence of remarkable improvement. Considering calcium intakes quantitatively, therefore, the present results suggest that a positive balance could be obtained in Chinese adults with calcium intakes as low as 300 mg/d with plant-based diets, according to the results derived from the meta-regression model of balance by intake. The findings are in contrast to the results from Europeans and Americans that have reported much higher calcium intakes required for the acquisition of a neutral balance.[13,14,28]

Table 1. Characteristics of the metabolic studies include

Study name	Region	Sex	Age (years)†		Period	Duration (days)††		Diet	Number of individual balances
			Mean	SD		Adaptation	Balance		
Adolph,1932[16]‡¶	Peiping								
n=3		M, F	(18-27)		3	3	4	Typical northern China diet (soy bean curd 210 g/d)	3
Kung,1937[17]‡	Peiping								
n=5		F	21.8	0.8	1~3	4	3×4	Ordinary Chinese diet + fruit	15
Kung,1938[18]‡¶	Tsining								
n=8		M	19.0	1.2	1~2	2	2×3	Regular school diet	15
Chu, 1941[19]‡¶	Peiping								
n=6		M	26.5	2.4	1~2		2×4	Self-chosen diet	6
n=6		F	25.2	1.8	1~2		2×4	Self-chosen diet	6
Hsu,1941[20]‡¶	Peiping								
n=3		M	20.3	1.8	1~2	3	2×3	Northern China cereal diet	4
Wang,1945[21]‡	Chungking								
n=6		M	28.7	6.4	1~2	2×3	2×4	Brown rice and vegetarian diet	12
Chen,1948[22]‡	Chungking								
n=3		M	(23-25)		1~4	4×3	4×7	Typical southern China diet	12
Chin,1958[23]‡	Peking								
n=60		M, F	(Adults)		1~9	9×3	9×5	Coarse cereal diet / mixed diet / refined grain diet	147
Liu,1988[24]¶	Peking								
n=5		M	(Adults)		1~2		2×4	Self-chosen diet (pre-bed rest)	5
Xie, 1990[25]	Changsha								
n=10		M, F	34.6	12.2	1	2	3	Typical southern China diet	10
Deng, 1993[26]§¶	Changsha								
n=10		M, F	(19-43)		1		2	Self-chosen diet	10
Li, 2007[27]	Liangshan								
n=12		M	(20-22)		1	3	9	Typical diet of Yi nationality	12

†Age range was given in parentheses if SD was not reported.
‡Sequential diet design; all subjects received one diet followed by a second diet. The included results from each of these sequential design studies, where the same subjects received multiple diets, were first summarized, so that each of them contributes only one data point to each meta-analysis.
§Randomized, double-blind, crossover design.
¶Calcium metabolic data for some periods were excluded for not meeting the inclusion criteria.



1. ID: individual calcium metabolic studies.
2. Dietary calcium intake:mean dietary calcium intake for individual calcium metabolic studies in an ascending sort order.
3. Calcium balance:calcium retention (mg/d).
4. X axis:calcium retention (mg/d).
5. Y axis:calcium metabolic studies with different dietaty calcium intakes.
6. Solid black diamond: mean calcium retention for each metabolic study.
7. Hollow cyan diamond: average calcium retention for subgroups or for all the studies.
8. Grey square: weight of each study.
9. Horizontal solid line: 95% CI of calcium retention for each study or for subgroups or for all the studies.
10. Vertical short-dash line: reference line of the average calcium retention for all the studies.
11. Vertical solid line: reference line of neutral calcium balance

Figure 2. Calcium retentions in Chinese adults with habitual dietary calcium intakes.

Table 2. Univariate meta-regression exploring the role of calcium metabolism on calcium retention

Calcium retention (mg/d)	β (95% CI)	Intercept	I^2 (%)	Adjusted R^2 (%)	*p* value
Dietary calcium intake (mg/d)	0.27 (0.09, 0.44)	-74.1	84.9	61.5	0.006
Urinary calcium excretion (mg/d)	-0.08 (-0.92, 0.76)	83.2	93.3	-11.6	0.829
Faecal calcium excretion (mg/d)	0.22 (-0.06, 0.50)	-8.3	89.6	24.4	0.110
Fractional calcium absorption (%)	1.44 (-3.29, 6.16)	24.2	92.8	-3.8	0.517

Table 3. Summary results and 95% CIs of calcium metabolic studies in Chinese adults grouped by four quartiles of dietary calcium intakes

Subgroups	Dietary calcium intake (mg/d)	Urinary calcium excretion (mg/d)	Faecal calcium excretion (mg/d)	Calcium retention (mg/d)	Fractional calcium absorption (%)
1st quartile	392 (315, 469)	79 (46, 112)	266 (196, 335)	45 (27, 64)	32.0 (22.4, 41.6)
2nd quartile	475 (433, 516)	169 (112, 226)	283 (231, 335)	18 (-18, 55)	39.3 (23.7, 54.8)
3rd quartile	649 (626, 672)	140 (71, 209)	409 (381, 437)	85 (-2, 171)	38.0 (35.6, 40.4)
4th quartile	915 (881, 948)	92 (0, 183)	658 (478, 838)	163 (13, 312)	27.4 (5.5, 49.2)
Overall	583 (515, 651)	117 (84,149)	381 (319, 442)	72 (38, 107)	33.3 (28.1, 38.6)

Calcium retention differences

The available data in Chinese adults consuming self-chosen or typical Chinese diets in this paper show that 300-1,000 mg is the approximate range of daily dietary calcium intakes. All the aggregate calcium retentions are positive, and more than 75% of the dietary calcium intakes did not reach 800 mg/d,[10,11] the Chinese recommendation allowances for calcium. Derived from 19 feeding studies undertaken by the USDA between 1976 and 1995, in 155 American men and non-pregnant women within 20-75 years of age with daily intakes of calcium ranging from 415 to 1,740 mg, Hunt and Johnson defined a neutral calcium balance at intakes of 741 mg/d, which formed the basis of the Institute of Medicine (IOM) 2011 Dietary Reference Intakes (DRIs) for calcium.[13] Food and Agriculture Organization (FAO)/ World Health Organization (WHO) examined data from 210 available high-quality published calcium balances in 81 individuals in developed countries, the basis of the FAO/WHO recommendations published in 2004, and the calcium intake at which urinary calcium was equal to the net absorbed calcium was 520 mg/d by using nonlinear regression model.[14] Nordin and Morris recalculated the equilibrium of 157 calcium balances in adult men ≤59 years of age, and equilibrium was reached at an intake of 535 mg/d.[28] However, in our previous meta-regression analysis, we reported an intake of 400-500 mg/d at zero balance, varying from statistical models, for healthy Chinese adults aged between 18 and 60 years.[12] When a positive balance is obtained in this paper, the dietary calcium intake of Chinese adults is notably lower than that of Europeans and Americans.

Calcium metabolism and adaptation

Calcium as a nutrient is important for skeleton growth. A rise from about 26 to 30 g at birth to approximately 1,200 g in women and 1,400 g in men at maturity,[29-31] requiring an average daily calcium retention of 180 mg during the first 20 years of growth.[14] In addition to adjusting dietary supply, the body can meet calcium requirements of individuals during physiology cycle by regulating calcium absorption and excretion. Calcium retention is determined by the relationship between calcium intake and calcium absorption and excretion.[14]

In this paper, the average fractional calcium absorption among Chinese adults is about 33% at an intake of about 600 mg/d calcium, which is approximately 10% higher than their American counterparts whose average calcium intake is more than 800 mg/d.[13] Besides, the fractional calcium absorption remains at a high level with little changes when the calcium intake ranges between 300 and 1,000 mg/d, in accordance with results deriving from recent studies.[32,33] This contrasts with that in Caucasian, whose fractional calcium absorption reaches a peak of some 35% at an intake of about 400 mg, and then falls off as intake increases further to a level of 20% with an intake of approximately 1,000 mg.[14] Excluding the impact of errors in sampling and testing, it indicates dietary calcium is likely be utilized more efficiently in Chinese than in Westerners.

Assuming the relatively constant fractional calcium absorption, calcium retention increases with calcium intake. Since high calcium intakes may not represent for the daily diets of the subjects, this higher retention might result from adaptation to low calcium diets. However, from the current stand-point, it is hard to clarify whether the high calcium retention would last for a long term and higher calcium retention would yield clinically significant benefits.

Urinary calcium excretion varies in a wide range and may be affected by numerous errors. The mean daily calcium loss of Chinese adults via renal excretion is about 120 mg, which is almost half of that reported in developed countries.[34] Faecal calcium excretion depends on calcium intake and fractional calcium absorption. Although our results show a similar trend of faecal calcium excretion increasing with calcium intake, the increase is slightly lower than that in Americans.[13] These decreased calcium excretions maybe another physiological adaptation to low calcium diets.

Representativeness of experimental diets for habitual calcium intakes

In retrospect, the composition of the experimental diets differed across studies. It seems not permissible to neglect these large extent differences. Generally, the calcium sources of Chinese adults were plant-based foods, although the variety in food components is inevitable. Accordingly, we enrolled the calcium metabolic studies in which experimental diets were close to usual diets in both quality and quantity and removed studies with adding components (such as calcium supplements and amino acids), and unusually large quantities of staple food or non-staple food. In terms of daily dietary calcium intakes, the typical intake level in Chinese is between 300 and 600 mg. Those, with calcium intakes of almost 900 mg/d, sourced from vegetables or cereals as shown in the recipes were included. While high dietary calcium intakes may not be common among Chinese, it is a way to obtain a wide range of calcium retention data by involving those special cases in this paper.

Heterogeneity of included studies

There is a substantial heterogeneity in the pooled calcium retention. However, only dietary calcium intake is significantly associated with the heterogeneity from the analysis of univariate meta-regression, which account for almost 2/3 of the heterogeneity. Whereas other factors such as urinary calcium excretion and fractional calcium absorption did not have any prominent effect on the heterogeneity. Dietary calcium intakes and faecal calcium excretion are the key comparative variables in this study. Difference within these two variables shall not be an indicator of heterogeneity. Thus we ignored the heterogeneity derived from these two variables.

Limitation

It is unpredictable that the impact of the variation of nutritional status, dietary behaviour and life style of Chinese during past century on the present data synthesis. Therefore the conclusion of this study is only applicable to the traditional plant-based diets and habitual low-calcium intakes. The four calcium metabolic studies published after 1988 including 37 individuals, showed similar met-

abolic characteristics at a similar calcium intake level, compared with that of the early published studies. The results agree to the rationality of our pooled analysis. In other words, they suggested that Chinese adults living between 1930s and 1950s could maintain a positive calcium balance at the calcium intakes of about 300 mg/d, and they also implied that there was no evidence showing that nowadays Chinese were incapable of maintaining a positive calcium balance at the habitual calcium intake level.

In this analysis, we did not take other factors that may affect calcium metabolism (e.g. exercise, season, and vitamin D status) into account for more complete information. Since the calcium metabolic studies were conducted by different authors, in different decades and in different experimental conditions (e.g. study environment, study duration, sample collection and analysis), calcium metabolic data collected using similar tightly controlled experimental procedures are required.

A critical concern in this study is that all the analyses are population-based and may not be generalizable to the nutritional status of individuals.

Conclusion

The Chinese adults pooled in the present study appear able to maintain a positive calcium balance with plant-based diets at calcium intakes as low as 300 mg/d, via a possible adaptation in calcium metabolism to increase fractional calcium absorption and decrease calcium excretion in urine and faeces.

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AUTHOR DISCLOSURES

The authors have no conflict of interest in regards to this paper.

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Original Article

Habitual dietary calcium intakes and calcium metabolism in healthy adults Chinese: a systematic review and meta-analysis

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中国健康成人在习惯性膳食钙摄入水平下的钙代谢：系统综述和荟萃分析

为了探讨中国人与西方人之间钙需要量的代谢差异，我们系统地研究了中国成人在习惯性膳食钙摄入水平下的钙代谢特点。从 PubMed、Cochrane Library、中国生物医学文献数据库（SinoMed 中心网络版）、全国报刊索引数据库—篇名库及相关论文和期刊的参考文献，检索 2015 年 3 月 17 日之前发表的 18-60 岁中国健康成人在典型中国膳食条件下的钙代谢试验。采用结构式数据库提取报道了钙摄入量、钙储留量、尿钙排出量、粪钙排出量和/或表观钙吸收率的代谢试验信息。采用随机效应荟萃分析模型汇总数据。在检索到的 2,046 篇文献中，有 12 个研究符合纳入标准，包括由 137 名受试者的 257 条个体数据汇总得到的 13 条聚合数据。分析以自选膳食或者典型中国膳食为试验餐的代谢数据。各研究平均膳食钙摄入量介于 288-948 mg/d 之间，平均钙储留量介于 13-294 mg/d 之间。汇总的膳食钙摄入量、尿钙排出量、粪钙排出量、钙储留量和表观钙吸收率分别为 583 mg/d、117 mg/d、381 mg/d、72 mg/d 和 33.3%。膳食钙摄入量和粪钙排出量共解释了约 85%的钙储留量异质性。以植物性膳食为主的中国成人在钙摄入量低至 300 mg/d 时仍能通过增加表观钙吸收率和减少尿粪钙排出量来维持正钙平衡。

关键词：钙代谢、中国成人、植物性膳食、荟萃分析、系统综述