



FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

Systematic Review of the Evidence for a Relationship between Chromium and Glycaemic Control

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Executive Summary

Part One

Review question Part One: chromium ‘deficient’ population	
Food-health relationship	Increased intake of chromium decreases blood glucose concentrations in people who are deficient in chromium
GRADE rating	Not assessable
Component	Notes
Body of evidence	Fourteen studies described the relationship between chromium and glucose levels in participants described to be ‘chromium deficient’ by the study authors. However, in most of the studies chromium status of the participants was not clearly described. We considered that the participants in nine of the 14 studies were unlikely to be ‘chromium deficient’. The remaining five papers described case reports that outline the effects of intravenous (IV) chromium intervention in patients receiving long term total parenteral nutrition (TPN). The IV dose of chromium ranged from 150–250 µg/d, administered over a period of 14 to 16 days.
Consistency	All included studies report apparent favourable effects of chromium on blood glucose concentrations; however, the effect could be influenced by the numerous confounding factors present in the included case reports. Quantitative evaluation of the data was not possible due to the lack of appropriate data. The possibility of publication bias in this body of evidence is considered large, considering the designs of included studies. Reports of cases and case series are more likely if the cases had positive outcomes, while reports with negative outcomes are less likely
Causality	The evidence base for chromium treatment in the ‘chromium deficient’ population mostly originates from case reports or case series. These studies are limited in being able to assess the causality of chromium treatment on blood glucose concentrations. Causality of the relationship is not established. In addition, the biological plausibility of chromium affecting blood glucose concentrations is uncertain.
Plausibility	There are multiple hypotheses proposed for the effect of chromium on blood glucose concentration in the ‘chromium deficient’ population; however, no established mechanism of action is evident from the current literature.
Generalisability	The study population described by the included studies were patients with complicated medical conditions, requiring long term TPN. Therefore the results of this systematic review cannot be generalised to the Australian and New Zealand general populations.

There was no existing meta-analysis or systematic review that assessed the relationship between chromium treatment and blood glucose concentrations in people who are deficient in chromium.

Therefore, we undertook a new systematic review. Five relevant studies (Brown et al. 1986; Freund et al. 1979; Jeejeebhoy et al. 1977; Tsuda et al. 1998; Verhage et al. 1996) were included.

All of the included studies were at a high risk of bias due to the existence of numerous confounding factors.

There was either a lack of a control group and/or meaningful data within the included studies.

The results presented in the study participants could not be generalised to the Australian and New Zealand populations.

Furthermore, chromium was administered intravenously in all included studies; the form and dose of chromium administration cannot be extrapolated to represent a food-health relationship.

Therefore, we consider the relationship between dietary chromium and blood glucose levels in a 'chromium deficient' population to be not assessable at this time.

Executive Summary

Part Two

Review question Part Two: free-living population	
Food health relationship	Increased intake of chromium decreases blood glucose concentrations in normoglycaemic or impaired glucose tolerant people who are consuming a wide range of foods
GRADE rating	No effect: Moderate ⊕⊕⊕
Component	Notes
Body of evidence	A recent systematic review and meta-analysis of randomised controlled trials (RCT) was updated. The trial included normoglycaemic and impaired glucose tolerance populations .
Consistency	The majority of the included RCT presented a low risk of bias and was moderate or high quality. Balk et al. (2007) and the review authors confirmed this. The included comparisons were consistent in showing no effect of chromium treatment on blood glucose levels in normoglycaemic or impaired glucose tolerance populations. Together with low statistical heterogeneity in both meta-analyses, there is a strong indication of consistency for no relationship between chromium and blood glucose levels.
Causality	A causal relationship between chromium and blood glucose concentrations was not established. RCT were included because they are a strong design for determining causality of a relationship. Given the meta-analyses in both normoglycaemic and impaired glucose tolerance populations showed no effect of chromium on blood glucose levels, the degree of certainty for no causal relationship is 'Moderate'.
Plausibility	Multiple hypotheses have been proposed for the effect of chromium on blood glucose concentration in the free-living population; however, no established mechanism of action for the beneficial effects of chromium has been demonstrated in the current literature.
Generalisability	The non-effect of chromium on blood glucose levels is relevant for normoglycaemic and impaired glucose tolerance adult populations. One study in normoglycaemic, overweight children suggests that the non-effect of chromium treatment may also be applicable for children also.

A number of systematic reviews and meta-analyses of RCT exploring the effect of chromium supplementation on blood glucose levels were available for update.

The review by Balk et al. (2007) was identified to be suitable to update for the purpose of the present review.

At the time of Balk et al.'s review 19 RCT (providing 22 strata) in normoglycaemic populations and 7 RCT (providing 9 strata) in populations with impaired glucose tolerance were included for meta-analysis.

In the systematic review update, three new relevant studies were included since the review by Balk et al. (2007); two studies conducted in adults with impaired glucose tolerance (Ali et al. 2011) or metabolic syndrome (Iqbal et al. 2009) and another in normoglycaemic, overweight children (Kim et al. 2011).

Meta-analyses of data in normoglycaemic and impaired glucose tolerance populations indicate no effect of chromium on blood glucose levels.

No serious concerns of study biases, inconsistency, imprecision or other methodological issues were identified from the current evidence.

However, the studies were of relatively short duration and so no conclusions can be drawn about whether longer administration might have an effect.

Therefore, we conclude that there is a 'Moderate' degree of certainty for no relationship between chromium intake and blood glucose levels in both normoglycaemic and impaired glucose tolerance populations.

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1 Introduction

In 2010, the health claim 'Chromium contributes to the maintenance of normal blood glucose levels' was substantiated based on a Scientific Opinion by the European Food Safety Authority (EFSA) (EFSA Panel on Dietetic Products Nutrition and Allergies 2010, 2011). The claim was subsequently authorised by the European Union (European Commission, Regulation 432/2012 of 16 May 2012). The scientific evidence that the Opinion cited consists of primarily case studies or case series in persons receiving TPN (Brown et al. 1986; Freund et al. 1979; Jeejeebhoy et al. 1977) or malnourished infants (Gurson and Saner, 1971). In long-term TPN patients, blood glucose concentrations were restored to normal levels upon the addition of chromium to the patients' nutrition supply. Whether the beneficial effects of dietary chromium on glycaemic control are translatable and applicable for the Australian and New Zealand general population is currently unclear.

It is unclear whether EFSA has conducted a systematic review on the relevant evidence base; no previous systematic review was identified for the effects of chromium on glycaemic control in people who are chromium deficient. Previous systematic reviews evaluating the effects of dietary chromium supplements on glycaemic control show no beneficial effects in healthy populations with normal glucose control (Althuis et al. 2002; Bailey 2014; Balk et al. 2007). In patients with Type 2 diabetes mellitus (DM), there is some evidence for improvements in fasting blood glucose and glycated haemoglobin (HbA1c) after chromium supplementation (Balk et al. 2007; Patal et al. 2014; Yin and Phung 2015). However, the results from previous meta-analyses are not in agreement (Althuis et al. 2002; Bailey 2014) due to discrepancies in search strategies, inclusion criteria and statistical methods. No previous systematic reviews were identified for the effect of chromium on glycaemic control in people who are chromium deficient.

1.1 Property of food/food

Chromium is a mineral that is primarily found in two forms, trivalent chromium (Cr^{3+}), which is biologically active and found in food; and hexavalent chromium (Cr^{6+}), a carcinogen often found in industrial pollution. This report will consider only the effects of trivalent chromium found in food or supplements in a variety of forms, such as chromium (III) picolinate, chromium (III) chloride or chromium (III) potassium sulphate. Trivalent chromium has been proposed to be necessary for the action of insulin in energy metabolism, particularly in the management of blood glucose concentrations. In 2006, the Nutrient Reference Values working group concluded that insufficient data were available to set an Estimated Average Requirement (EAR) for chromium (National Health and Medical Research Council (NHMRC) and NZ MoH 2006) therefore Adequate Intake (AI) values for Australia and New Zealand were derived from estimates identified in the FNB:IOM review (Institute of Medicine 2001).

Chromium is widely distributed in food. In the 22nd Australian Total Diet study, the highest quantities of chromium were found in milk chocolate (9 µg), chocolate cake (12 µg), ham (13 µg), parsley (13 µg) and salt (10 µg) on a per 100 g basis. The mean intakes ranged from 20-36 µg/day for people 2 years and older (Food Standards Australia New Zealand 2008). However, due to the lack of EAR for chromium, limited conclusions were drawn for the adequacy of chromium intake in the Australian population.

Unless expressly permitted, foods cannot be fortified with chromium in Australia and New Zealand. Formulated meal replacements standardised under Standard 2.9.3 (Formulated meal replacements and formulated supplementary foods) and food standardised under 2.9.4 (Formulated supplementary sports foods) are permitted to be fortified with chromium.

Foods can make 'source of chromium' nutrition content claims if they contain at least 10% of the regulatory Estimated Safe and Adequate Daily Dietary Intake (ESADDI) per serving of food, or 'good source' claims if they contain at least 25% of the ESADDI per serving. The ESADDI for those aged 4 years and older is currently 200 µg and is derived from the 1989 US Recommended Daily Allowance. The more recent Adequate Intake of 35 and 25 µg/day in men and women, respectively, (NHMRC and NZ MoH 2006) has not yet been adopted into the *Australia New Zealand Food Standards Code*. For formulated meal replacements, the maximum claim permitted is 34 µg (17% of the ESADDI) per one-meal serving. For formulated supplementary sports foods, the maximum claim permitted is 100 µg of inorganic chromium or 50 µg of organic chromium per one-day quantity of the food.

There is one pre-approved relationship regarding chromium in Schedule 4 of the *Australia New Zealand Food Standards Code* that can be used to generate general level health claims about foods that can meet the criteria for making at least a source of chromium claim.

The bioavailability of chromium for humans is low (0.4–2.5% elemental chromium absorbed) (NHMRC and NZ MoH 2006). Recent studies of the pharmacokinetics of chromium compounds in rats revealed that the whole body retention of chromium 7 days after oral administration was 5 times higher from chromium chloride compared to chromium picolinate or chromium nicotinate (Laschinsky et al. 2012). The differences in chromium absorption for different chromium complexes in humans are unclear.

The safety of chromium (III) supplements has been under question and in a recent report describing the effect of chromium (III) on adipocytes, the antidiabetic activity of chromium (III) was attributed to the formation of reactive and carcinogenic chromium (V) and (VI) (Wu et al. 2015). The long-term effects of chromium supplementation on chromium-induced cancer and oxidative stress in humans remain unclear and require further investigation to establish the safety of chromium (III) supplementation.

1.2 Health effect

The health effect examined in this review was that chromium intake improves glycaemic control. Glycaemic control can be assessed by numerous measures, including blood glucose levels and glycated haemoglobin A1c (HbA1c). Blood glucose is the most commonly used marker of glycaemic control; increased levels of blood glucose concentration can be indicative of DM. HbA1c is used as a long term marker of glycaemic control as it reflects average blood glucose levels over a longer time period. Therefore, improvement in glycaemic control as indicated by reductions in blood glucose levels and HbA1c is considered to be a beneficial health effect.

Glucose concentration can be measured in whole blood, serum or plasma, at fasting or under non-fasting conditions. The World Health Organization (WHO) provides definitions of a range of blood glucose concentrations that can be used to assess diabetic status (WHO 2016). WHO (2016) considers impaired glucose tolerance (IGT) to be defined by a fasting plasma glucose concentration of < 7 mmol/L, and plasma glucose concentration of 7.8 – 11.1 mmol/L at 2 h after ingestion of a 75 g oral glucose load. Diabetes is considered to be defined by a fasting plasma glucose concentration of ≥ 7 mmol/L or plasma glucose of ≥ 11.1 mmol/L at 2 h after ingestion of a 75 g oral glucose load.

HbA1c is the measure of glycated haemoglobin (A1c) in the blood, and is often expressed as a percentage or proportion of total haemoglobin. HbA1c levels of ≥ 6.5% are considered to define diabetes (WHO 2016).

1.3 Proposed relationship

The food-health relationships assessed in this report are:

- Increased chromium intake reduces fasting blood glucose concentration in people with chromium deficiency
- Increased chromium intake reduces fasting blood glucose concentration in normoglycaemic or impaired glucose tolerant people consuming a wide range of foods.

2 ‘Chromium Deficient’ Population – Existing systematic reviews

No previous systematic reviews were identified for the relationship between chromium and glycaemic control in the chromium deficient population. A new systematic review was conducted to determine the proposed food health relationship in the chromium deficient population.

3 Free-Living Population – Summary and critical appraisal of existing systematic reviews

A number of systematic reviews and meta-analyses of RCT have been conducted to determine the effects of chromium supplementation on glycaemic control in normoglycaemic and Type 2 DM populations. In a systematic search of the literature (using the search strategy as indicated in 4.1), eight potential systematic reviews of RCT on the topic were retrieved, of which six reports included meta-analyses on the effects of chromium supplementation on measures of glycaemic control. Tables 1 and 2 summarise the characteristics and primary outcomes of previous systematic reviews.

Table 1: Characteristics of previous systematic reviews summarising the effects of chromium supplementation on glycaemic control

Authors	Year	Search strategy	Inclusion criteria	Interventions	Outcomes
Althuis et al. (2002)	2002	Cochrane Register, MEDLINE (1966-2000) Search terms: chromium, diabetes, glucose, insulin, haemoglobin A1c	Normoglycaemic, glucose intolerance or Type 2 DM Randomly assigned to dietary Cr supplementation or control (Excluded Anderson 1997; study conducted in non-Western country and inclusion of study brings statistical heterogeneity close to significance)	Chromium vs placebo or control	Fasting glucose, insulin, OGTT (glucose and insulin at 120 min.)
Bailey (2014)	2014	MEDLINE and Cochrane Controlled Trials Register (inception – February 2013) Search terms: chromium and diabetes or fasting glucose	Adults, with or without DM (excluded children) RCT of Cr supplementation English language Exclusion: studies with insufficient data to calculate pre-intervention standard error (SE) as well as pre-intervention and post-intervention blood glucose levels, cross-over trials that did not counterbalance carry-over effects of Cr supplementation (Excluded Pei 2006; “extremely large and unrealistic effect size”)	Chromium vs placebo	Fasting glucose
Balk et al. (2007)	2007	MEDLINE and Commonwealth Agricultural Bureau (inception – August 2006) Search terms: chromium, DM, glycaemia, glycosylated haemoglobin, metabolic syndrome, insulin resistance	Normoglycaemic, impaired glucose tolerance and Type 2 DM RCT of Cr supplementation ≥ 3 weeks, with ≥ 10 participants receiving Cr	Chromium vs placebo	HbA1c, fasting glucose, post-load glycaemia, insulin sensitivity
Patal et al. (2010)	2010	MEDLINE, Cochrane and Herdin (no dates provided) Search terms: chromium picolinate and DM	Type 2 DM RCT of chromium picolinate supplement intake of ≥ 3 months	Chromium picolinate vs placebo	HbA1c, fasting sugar, 2-h postprandial blood sugar, fasting insulin, lipid levels

Authors	Year	Search strategy	Inclusion criteria	Interventions	Outcomes
Suksomboon et al. (2014)	2014	MEDLINE, Cochrane library, CINAHL, Web of Science, Scopus, clinicaltrials.gov (to May 2013) MeSH terms and keywords: chromium, DM, diabetic, glycosylated haemoglobin, HbA1c, glucose and lipids	Type 1 or Type 2 DM RCT comparing Cr mono- or combined supplementation against placebo At least 3 weeks when reporting fasting plasma glucose, or at least 8 weeks if HbA1c was reported	Chromium (any form) mono- or in combination vs placebo	HbA1c, fasting plasma glucose
Yin and Phung (2015)	2015	PubMed, Embase, Cochrane library (inception to November 2014) Search terms: chromium and Type 2 diabetes	Patients with Type 2 DM RCT or observational studies Cr supplement of any dose or form Report HbA1c or fasting plasma glucose	Chromium (any form) vs placebo	Fasting plasma glucose, HbA1c

DM, diabetes mellitus; RCT, randomised controlled trials

Table 2: Primary outcomes determined by meta-analyses of previous systematic reviews

Authors	Year	Study Population	No. of included studies	Total no. of participants	Results			
					Outcome	Intervention	Strata	Effect Size (95% CI)
Althuis et al. (2002)	2002	Normoglycaemic (or with impaired glucose tolerance)	14	425	Fasting glucose	Cr (all forms)	10	0.028 mmol/L (-0.086, 0.14)
		Normoglycaemic + Type 2 DM	14	463	Fasting glucose	Cr (all forms)	14	0.027 mmol/L (-0.09, 0.15)
Bailey (2014) ¹	2014	Type 2 DM	8	440	Fasting glucose	Cr (all forms)	9	-0.05 (-0.24, 0.15)
		Normoglycaemic	9	369	Fasting glucose	Cr (all forms)	9	-0.11 (-0.11, 0.32)
		All	16	809	Fasting glucose	Cr (all forms)	18	0.02 (-0.12, 0.26)
Balk et al. (2007)	2007	Type 2 DM	11	381	HbA1c	Cr (all forms)	14	-0.6% (-0.9, -0.2)
		Type 2 DM	17	606	Fasting glucose	Cr (all forms)	22	-1.0 mmol/L (-1.4, -0.5)
		Glucose intolerance	7	148	Fasting glucose	Cr (all forms)	9	-0.1 mmol/L (-0.2, 0.1)
		Healthy	19	297	Fasting glucose	Cr (all forms)	22	0 mmol/L (-0.1, 0.1)
Patal et al. (2010)	2010	Type 2 DM	6	671	HbA1c	Cr picolinate	8	-0.7% (-0.73, -0.68)
					Fasting glucose	Cr picolinate	5?	-0.7 mmol/L (-0.74, -0.65)
Suksomboon et al. (2014)	2014	DM (mostly Type 2)	14	1179	HbA1c	Cr (all forms) mono + combo	17	-0.55% (-0.88, -0.22)
			24	1683	Fasting glucose	Cr (all forms) mono + combo		-1.15 mmol/L (-1.84, -0.47)
			13	816	HbA1c	Cr (all forms) mono	15	-0.58% (-0.93, -0.23)
			22	1284	Fasting glucose	Cr (all forms) mono		-1.13 mmol/L (-1.97, -0.3)

Authors	Year	Study Population	No. of included studies	Total no. of participants	Results			
					Outcome	Intervention	Strata	Effect Size (95% CI)
Yin and Phung (2015)	2015	Type 2 DM	14	875	Fasting glucose	Cr chloride	3	-0.37 mmol/L (-1.48, 0.73)
						Cr picolinate	4	-0.47 mmol/L (-1.22, 0.28)
						Cr yeast	3	-0.82 mmol/L (-1.89, 0.26)
						Brewer's yeast	3	-1.07 mmol/L (-1.96, -0.18)
					HbA1c	Cr chloride	1	N/A
						Cr picolinate	4	-0.6% (-1.32, 0.82)
						Cr yeast	3	-0.25% (-1.07, 0.57)
						Brewer's yeast	3	-0.71% (-2.29, 0.87)

[†] Effect sizes provided are standardised means

Based on the clarity of methodology and the primary outcomes presented, we identified two systematic reviews (Althuis et al. 2002; Balk et al. 2007) available that may be suitable for updating in the present report. In 2002, Althuis et al. completed a review of the effects of chromium supplements on glucose and insulin responses in “healthy” (including those with normal glycaemic control and impaired glucose tolerance) and Type 2 DM populations.

At the time of review, the authors identified 20 reports of RCT, with a total of 618 participants. In a meta-analysis assessing the effect of chromium on glycaemic control, Althuis et al. (2002) excluded a large study (Anderson et al. 1997) of 155 Chinese patients with Type 2 DM, stating that the inclusion of this study brings the P-values for heterogeneity below or very close to 0.05 and also that the study “was conducted in a non-Western country and it may represent the effect of supplementation in a chromium deficient population.”

We are unsure about the validity of the exclusion reasons. Based on their analysis, Althuis et al. (2002) concluded that chromium supplementation has no effect on glucose or insulin concentrations in healthy subjects. The limited available data (2 studies) for the DM population produced inconclusive results; the exclusion of Anderson et al.’s study, which showed significant decline in fasting blood glucose, may have underestimated the effects of chromium on glycaemic control.

Balk et al. (2007) conducted a similar systematic review and meta-analysis on the effects of chromium on glucose metabolism and lipids in 2007, with slightly different inclusion/exclusion criteria and statistical analyses to Althuis et al. (2002). The authors identified 41 studies that met their inclusion criteria, including the study (Anderson et al. 1997) that the Althuis et al. review excluded. Upon meta-analysis of the included reports, Balk et al. (2007) concluded no effect of chromium in glucose metabolism for people without DM, specifically, 0 mmol/L change (95% CI: -0.1, 0.1) in normoglycaemic population and -0.1 mmol/L change (95% CI: -0.2, 0.1) in people with glucose intolerance. For participants with Type 2 DM, chromium supplementation significantly decreased HbA1c by 0.6% (95% CI: -0.9 to -0.2) and fasting glucose concentrations by -1.0 mmol/L (95% CI: -1.4 to -0.5). The authors noted that larger effects were more likely to be observed in poor-quality studies and that the evidence is limited by poor study quality and heterogeneity in methodology and results, therefore the beneficial effects of chromium supplementation on glycaemic control in the DM population is uncertain.

There are other meta-analyses that have not been considered for updating as they only examined chromium supplementation in participants with DM (Patal et al. 2010; Suksomboon et al. 2014; Yin and Phung 2015). As the focus of this review is to assess the effects of chromium on blood glucose levels in chromium-deficient and normoglycaemic and glucose-intolerant populations, conclusions drawn by these meta-analyses in participants with DM are not appropriate. Although the meta-analysis by Bailey (2014) did examine the effects of chromium on normoglycaemic participants, Bailey’s review was not selected for update, despite being recent, because of the exclusion of studies that did not provide sufficient data to calculate pre-intervention standard errors or pre-intervention and post-intervention mean fasting glucose levels. The exclusion criteria in Bailey’s review resulted in only 18 studies being included in the meta-analysis, compared to 41 studies for the review by Balk et al. (2007).

Given the date of review, search strategy and the number of included studies, we have updated the review by Balk et al. (2007). The search strategy and inclusion criteria for the literature review were applied as described in the previous review (Balk et al. 2007). To ensure all eligible studies were included, we completed an independent hand search (described in 4.1) to ensure that the search strategy utilised by Balk et al.(2007) captured all applicable studies.

3.1 Review methods of Balk et al. (2007)

Balk et al.(2007) conducted a literature search of MEDLINE and Commonwealth Agricultural Bureau databases through to 8 August 2006. Search terms included chromium, DM, glycaemia, glycated haemoglobin, metabolic syndrome, insulin resistance and related terms. The search strategy, selection criteria and method of study selection were appropriate for identifying studies relevant in addressing the research question.

For inclusion in the review, studies were required to be RCT using chromium supplements, of any formulation. Parallel and cross-over study designs were included. Trials that involved supplementation periods of less than 3 weeks were excluded, presumably to exclude transient effects of chromium. Participants included individuals with Type 1 or Type 2 DM, glucose intolerance or normal glucose tolerance, as defined by the WHO or American Diabetes Association (ADA) criteria. Studies that included less than 10 participants in the chromium supplementation group were excluded; although other systematic reviews did not apply this exclusion criterion, Balk et al. (2007) has not excluded otherwise eligible studies. No specific exclusion was given for the age of participants. Table 3 summarises the inclusion/exclusion criteria of the Balk et al. (2007) review.

Table 3: PICOTS criteria for literature review of studies as per Balk et al.'s 2007 review

Population	Individuals with Type 1 or Type 2 DM, glucose intolerance or normal glucose tolerance (≥ 10 participants receiving chromium)
Intervention	Chromium supplements (all formulation)
Comparator	Control group
Outcome	Glycaemic control (glycated haemoglobin, fasting glucose, post-load glycaemia, insulin sensitivity)
Time	≥ 3 weeks duration of supplementation
Study design	Randomised controlled trials

Statistical analyses were completed using the net difference between the within-treatment (chromium supplementation) effect and the within-placebo effect. Random effects meta-analysis models were used to quantify the effects of chromium supplementation on glycated haemoglobin and fasting glucose. Where necessary, the authors estimated the SE of net change from the reported variance data, including *P*-values. In RCT with multiple treatment arms, the same control group data were used for multiple comparisons of treatment effect. Comparisons were excluded from meta-analyses if the paper did not have data on the variance of effect. Secondary analyses were conducted according to the formulation of chromium supplement. The authors also investigated the effects of study quality and funding sources on the reported effect sizes of individual studies in secondary analyses. Quality of included studies was assessed using a 3-level classification, according to the US National Kidney Foundation quality assessment tool (National Kidney Foundation 2002).

We have noted a number of limitations in Balk et al.'s meta-analyses, in particular with the reporting of statistical analyses. Details regarding statistical heterogeneity and the statistical program used were not provided in the published paper. Furthermore, potential publication biases within the meta-analyses were not assessed. Although the doses of chromium supplementation were provided in the forest plot of overall meta-analyses, the dose-response effect of chromium was not explored in a quantitative statistical method, for example meta-regression. These issues were addressed in the update of this systematic review.

3.2 Summary of results of Balk et al. (2007)

Balk et al. identified 41 studies that met their inclusion criteria (Table 3). Thirteen studies (providing 14 comparisons, $n = 381$) were included in the meta-analysis of change in HbA1c of patients with Type 2 DM. Overall analysis showed a significant decrease of 0.6% (95% CI -0.9, -0.2) in HbA1c as a result of chromium supplementation. Balk et al. (2007) noted that 11 of 14 interventions found a null or statistically non-significant effect. Overall, statistical significance appears to be driven by one study (Anderson et al. 1997), where they reported also a greater reduction of HbA1c with increasing doses of chromium picolinate. Secondary analyses stratified by study quality and funding sources are summarised in Table 4. In participants with glucose intolerance, the four included studies reported no statistically significant effect of chromium supplementation on HbA1c. As only one out of the four included studies of participants with glucose intolerance reported numerical data results, meta-analysis of these comparisons was not conducted.

Table 4: Secondary analyses of the effects of chromium supplementation on HbA1c levels in participants with Type 2 DM, according to study quality and funding sources (Balk et al. 2007)

Variables	No. of studies, comparisons (n)	Mean difference % (95% CI) ¹
Study quality		
A (highest)	5, 6 (151)	-0.27 (-0.52, -0.01)
B	3, 3 (54)	-0.39 (-0.9, 0.13)
C	5, 5 (176)	-1.40 (-2.01, -0.76)
Funding source		
Industry	3, 3 (135)	-1.20 (-2.25, -0.14)
Non-industry	3, 3 (52)	-0.58 (-1.56, 0.45)
Did not disclose	7, 8 (194)	-0.30 (-0.54, -0.01)

¹ estimated from Figure 1 of Balk et al.'s review (Balk et al. 2007)

Fifteen studies (providing 21 comparisons, $n = 606$) were included in the meta-analysis of change in fasting glucose levels in patients with Type 2 DM. Overall analysis suggests chromium supplementation significantly decreased fasting glucose concentrations (-1.0 mmol/L, 95% CI -1.4, -0.5). Secondary analyses were performed grouped by the form of chromium given (Table 5). Supplementation with brewer's yeast provided significant reduction in fasting glucose (-1.1 mmol/L, 95% CI -1.6, -0.6), however, no clear dose effect was observed. Chromium picolinate also provided a significant effect on fasting glucose (-0.8 mmol/L, 95% CI -1.6, -0.6). No significant effect was found with chromium chloride supplementation.

In participants with glucose intolerance, 7 studies (providing 9 comparisons, $n = 148$) concluded that chromium supplementation provided no significant effect on fasting glucose (-0.1 mmol/L; 95% CI -0.1, 0.1). Nineteen studies (providing 22 comparisons, $n = 297$) were included in the meta-analysis of change in fasting glucose in participants with normal glucose tolerance, where no significant effect of chromium supplementation was observed (0 mmol/L; 95% CI -0.2, 0.1).

For HbA1c in participants with DM and fasting glucose in normoglycaemic participants or participants with DM, Balk et al. noted that greater favourable effects were more likely to be observed in poor-quality studies (B or C rating) compared to the high quality studies (A rating) ($P < 0.03$). This leads to the suggestion that the evidence is limited by poor study quality and heterogeneity in methodology and results, therefore the beneficial effects of chromium supplementation on glycaemic control are uncertain.

Table 5: Secondary analyses of the effect of chromium supplementation on fasting blood glucose in participants with diabetes mellitus, glucose intolerance or normal plasma glucose, according to chromium formulation, study quality and funding source (source: Balk et al. 2007)

Population health status	Variables	No. of studies, comparisons (n)	Mean difference mmol/L (95% CI)
Diabetes mellitus	Chromium formulation		
	Brewer's yeast	5, 6 (192)	-1.1 (-1.6, -0.6)
	Cr chloride	6, 7 (141)	-0.3 (-0.9, 0.2)
	Cr picolinate	7, 8 (295)	-0.8 (-1.2, -0.3)
	Cr milk powder	1,1 (58)	N/A
	Study quality ¹		
	A	3, 4 (122)	-0.68 (-1.2, -0.13)
	B	6, 7 (212)	-1.46 (-2.77, -0.14)
	C	7, 10 (272)	-0.75 (-1.28, -0.22)
	Funding source ¹		
	Industry	3, 4 (139)	-2.11 (-3.88, -0.34)
	Non-industry	7, 10 (289)	-0.75, (-1.20, -0.27)
	Did not disclose	6, 7 (178)	-0.6 (-1.09, -0.12)
Glucose intolerance	Chromium formulation		
	Brewer's yeast	1, 1 (13)	N/A
	Cr chloride	3, 5 (77)	0 (-0.2, 0.2)
	Cr nicotinate	2, 2 (29)	-0.8 (-1.8, 0.2)
	Cr picolinate	3,3 (51)	0 (-0.4, 0.4)
	Study quality ¹		
	A	1, 1 (20)	0.06 (-0.45, 0.58)
	B	4, 5 (69)	-0.1 (-0.37, 0.17)
	C	2, 3 (59)	-0.23 (-0.71, 0.28)
	Funding source ¹		
	Industry	3, 3 (51)	-0.26 (-0.58, 0.07)
	Non-industry	1, 2 (19)	0.17 (-0.42, 0.78)
	Did not disclose	3, 4 (78)	-0.01 (-0.25, 0.24)

Population health status	Variables	No. of studies, comparisons (<i>n</i>)	Mean difference mmol/L (95% CI)
Normoglycaemic	Chromium formulation		
	Brewer's yeast	5, 5 (52)	-0.2 (-0.4, 0.1)
	Cr chloride	11, 12 (194)	0.1 (-0.1, 0.2)
	Cr picolinate	3, 4 (43)	-0.1 (-0.5, 0.2)
	Cr milk powder	2, 2 (23)	Not reported
	Study quality ¹		
	A	0	N/A
	B	12, 15 (220)	0.02 (-0.1, 0.14)
	C	7, 7 (73)	-0.11 (-0.29, 0.06)
	Funding source ¹		
	Industry	3, 4 (41)	-0.01 (-0.4, 0.38)
	Non-industry	12, 13 (154)	-0.11 (-0.24, -0.02)
Did not disclose	4, 5 (102)	0.14 (-0.02, 0.32)	

¹ estimated from Figure 1, Balk et al.'s 2007 review.

3.3 Critical appraisal of Balk et al. (2007)

3.3.1 Study identification and selection

Search terms used were appropriate for the PICOTS question of this review. Balk et al. included studies that were designed as RCT of chromium supplementation that was ≥ 3 weeks in duration and involved ≥ 10 participants in the chromium treatment group. This is possibly used to exclude studies that examine the acute effects of chromium on glycaemic control and pilot studies that have small sample sizes; however, the exact reasons were not clearly stated in the paper. Treatments that involved chromium supplementation alone were included in the review; therefore the effects of treatment can be attributable to the food property of chromium. Furthermore, Balk et al.'s review included a range of chromium formulations that are found in food, which contributes to the strength of the review.

3.3.2 Assessment of bias

Balk et al. excluded supplementation studies that lacked a comparable control group or control period by selecting only RCT, thereby minimising selection bias. Balk et al. used a 3-level study quality classification system, based on the US National Kidney Foundation quality assessment tool (National Kidney Foundation 2002). Studies with least bias were given a quality rating of A; the study will have a clear description of the population, setting, appropriate reference standard, proper measurement techniques, appropriate statistical and analytic methods, no reporting errors and no obvious bias. A quality rating of B indicates that the study is susceptible to some bias but not sufficient to invalidate the results. Studies with significant bias that may invalidate the results were given a quality rating of C; these studies may have serious errors in design or reporting. Balk et al.'s assessment in the risk of biases of individual studies was appropriate for this review.

Balk et al. (2007) noted that the quality of studies identified in the review was generally poor and subject to bias as a result of the lack of blinding or allocation concealment, inadequate randomisation, high dropout rates, non-standard outcomes measurements and inadequate reporting of chromium intervention. In secondary analyses where studies were categorised by the quality score, Balk et al. observed greater beneficial effect of chromium supplementation on glucose outcomes in poor-quality (C rating) studies than in fair or good quality (A or B rating) studies. The authors also suggest that publication bias may exist within the literature, particularly with added conflicts of interest in industry-funded studies. However, Balk et al. did not explore potential publication bias by funnel plot assessments.

Balk et al. also completed secondary analysis of main outcomes stratified by funding source of the trials. The paper reports a trend towards greater net improvement in fasting glucose for participants with DM in studies that were funded by industry ($P = 0.06$).

3.3.3 Data extraction and analysis

Data extraction processes were appropriate; however, the statistical analyses presented by Balk et al. lacked assessment of statistical heterogeneity. The overall meta-analysis of treatment effect was determined by net difference of within-treatment (chromium supplementation) effect and within-placebo effect. Data from cross-over studies were extracted in the same manner as parallel trials, without explicit adjustments or considerations for carry-over effects.

There are a number of limitations within the review, specifically the lack of information provided in the conduct of meta-analyses. No information was provided regarding the name or source of the statistical program that was used to undertake the analyses. The

presentation of the meta-analysis was limited also by numerical data of individual studies, which makes validation of the results challenging. Given that Balk et al.'s results were mostly in accordance with other systematic reviews, the limitations identified in Balk et al.'s review are unlikely to impact the validity of the results or interpretation.

3.3.4 Data interpretation

From the overall results presented in meta-analyses, Balk et al. (2007) concluded that no significant effect of chromium was observed in people without DM. While significant improvements in glycaemic control were noted in participants with DM, the authors cautioned against making a definitive claim regarding the effect of chromium supplementation on glycaemic control, based on the quality of the evidence available.

The quantitative results were supported by Balk et al.'s assessment of study quality and potential study biases. Balk et al. (2007) used an appropriate study quality assessment tool that was designed to identify potential risk of biases in included studies. Furthermore, the extraction of information regarding funding source of individual studies in Balk et al.'s review further explored potential biases mediated by conflicts of interest. The assessments of these factors led to the Balk et al.'s comment that the evidence available was limited by poor study quality, heterogeneity in methodology and results and the lack of chromium status assessed.

3.4 Considerations of validity and strength of evidence

Overall, the systematic review and meta-analysis by Balk et al. addressed the food-health relationship using appropriate search strategies, data extraction and interpretation, although a number of limitations within the meta-analysis were identified, specifically in the reporting of results and statistical methods. Other systematic reviews and meta-analyses are broadly in agreement with Balk et al.'s results. Therefore, we consider that the limitations within Balk et al.'s review are unlikely to influence the conclusions drawn by the authors.

4 'Chromium Deficient' Population – Evaluation of evidence

The aim of the current review was to assess the evidence base that chromium affects glycaemic control in people who are deficient in chromium ('chromium deficiency' population). As no previous systematic reviews were identified, a new systematic literature search will be conducted.

4.1 Methods

4.1.1 Search strategy

PubMed, EMBASE and Cochrane Central were searched for original research papers published from inception to 28th May 2015, limited to human investigations and English language publications. Search terms used were "chromium" and terms related to glycaemic control, such as "glucose," "HbA1c." Relevant MeSH headings were used in relevant search databases. The full search strategy is described in Appendix 1.

Table 6 summarises inclusion/exclusion criteria of this review. Inclusion criteria include studies of 'chromium deficient' humans (as determined by the study authors) who were supplemented with chromium, via enteral or parental routes, and where measures of glycaemic control were investigated as a study outcome. Intervention studies – case reports, case series and clinical trials were included in the systematic review. Studies involving

chromium supplementation in non-deficient populations were excluded. Reviews, letters and editorials on the topic were excluded. Cross-sectional, cohort and case-control studies comparing chromium deficient population with free-living population were also excluded. The search output from individual electronic database was imported into EPPI-Reviewer 4 (<http://eppi.ioe.ac.uk/eppireviewer4/>), where the selection of included studies was completed.

Table 6: PICOTS criteria for studies of chromium supplementation in ‘chromium deficient’ population

Population	‘Chromium deficient’ humans
Intervention	Chromium supplementation (enteral or parenteral) as trivalent Cr
Comparator	For case studies, comparator is the same individual before Cr intervention was initiated. For trials, comparator is a control group or period
Outcome	Glycaemic control (fasting blood glucose, HbA1c)
Time	Any duration
Study design	Randomised controlled trials, clinical trials, case series or case reports

4.1.2 Investigators

Two investigators independently screened the search output for potential studies that provides evidence for a relationship between chromium and glycaemic control in ‘chromium deficient’ populations.

4.2 Results

4.2.1 Search results

The PRISMA flow chart details the number of studies screened and included in the review (Figure 1).

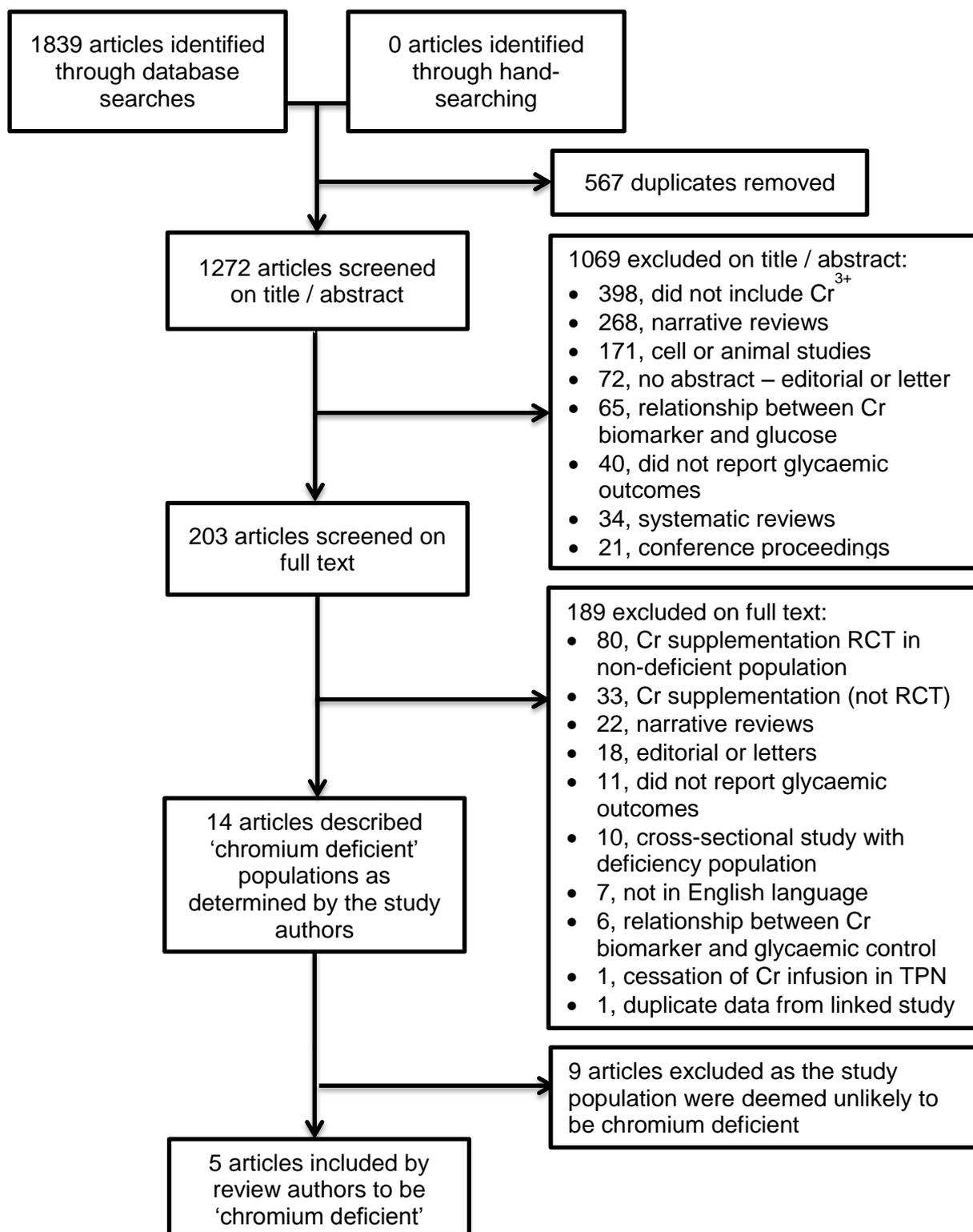


Figure 1. PRISMA flow chart describing the systematic review process for the 'chromium deficient' population

4.2.2 Included studies

Fourteen studies were identified that included study participants who were described to be potentially 'chromium deficient' by the study authors. However, we deemed the study populations in nine of those studies were unlikely to be chromium deficient, especially without the assessment of chromium status, in terms of dietary intake or biomarker. The 9 excluded studies mostly included participants who were infants with protein-energy malnutrition (Carter et al. 1968; Gurson and Saner, 1971; Hopkins et al. 1968) or acutely ill hospitalised patients (Anderson et al. 1988; Drake et al. 2012; Phung et al. 2010; Surani et al. 2012; Via et al. 2008; Wongseelashote et al. 2004). Details on the nine excluded studies are presented in Appendix 2.

The remaining five studies that are included in the current systematic review describe the effects of chromium supplementation on glycaemic control in 'chromium deficient' patients ($n = 5$) on long term TPN (Brown et al. 1986; Freund et al. 1979; Jeejeebhoy et al. 1977; Tsuda et al. 1998; Verhage et al. 1996). All five papers were case reports and therefore lacked a specific study objective. The age of the included participants ranged from 35-63 years, with both sexes represented ($n = 3/5$ females). Chromium interventions in all five included case reports were administered intravenously as part of the participants' daily TPN. The dose of IV chromium ranged from 150-250 $\mu\text{g}/\text{d}$, administered over a period of 14-16 days. Details of the included studies are provided in Table 7.

Table 7: Summary of study characteristics and findings for included studies using intravenous chromium interventions

Reference, study design	Participants	Interventions ¹	Potential Confounders	Results	Notes
Brown et al. (1986); case report	63 yo female with gangrenous distal small bowel and cecum; multiple small bowel resections leading to short bowel syndrome	IV CrCl ₃ with TPN (200 µg/d, 2 weeks); initiated 7 months after start of TPN	<ul style="list-style-type: none"> • TPN for last 7 months (1700 glucose calories and 85 g protein/d) • Insulin given (10-30 U/d) 	<ul style="list-style-type: none"> • Plasma Cr unchanged; improvements in serum glucose and exogenous insulin requirement after supplementation. 	<ul style="list-style-type: none"> • Glucose infusion reduced during chromium supplementation • Zinc supplementation also given • High jejunostomy loss (1500-2000 mL/d)
Freund et al. (1979); case report	45 yo female with mesenteric thrombosis; bowel resection	IV CrCl ₃ with TPN (150 µg/d for 16 d); initiated 8 months after the start of TPN	<ul style="list-style-type: none"> • TPN initiated at 3000-4000 calories/d, 2000 calories/d after 4 months • Insulin initiated (20-30 U/d) 	<ul style="list-style-type: none"> • Blood glucose decreased after Cr • Exogenous insulin requirement decreased after Cr • Serum Cr prior to intervention was 0.5 ug/dL; no measurement after Cr 	<ul style="list-style-type: none"> • Patient died of overwhelming sepsis shortly after
Jeejeebhoy et al. (1977); case report	40 yo female with mesenteric thrombosis; complete enterectomy	IV CrCl ₃ with TPN (250 µg/d for 2 weeks); initiated 5 y after the start of TPN	Symptom free for 3.5 y from start of TPN. 45 U/d insulin required before start of Cr treatment	<ul style="list-style-type: none"> • Improved fraction rate of glucose clearance in IVGTT after Cr • Exogenous insulin no longer required after Cr • Negative Cr balance found prior to treatment (blood Cr: 0.55 ng/mL, hair Cr: 154-175 ng/g dry weight) 	<ul style="list-style-type: none"> • Positive Cr balance achieved with Cr treatment • Continued with 20 µg/d Cr with TPN thereafter, patient remained well for 18 months
Tsuda et al. (1998); case report	35 yo male with idiopathic intestinal pseudo-obstruction	IV Cr with TPN, form not specified (200 µg/d for 2 weeks), initiated 13 y after starting TPN	TPN for 13 years; 500 g glucose, 10% amino acids, electrolytes, multivitamin and essential elements (Fe, Zn, Mn, Cu, I)	<ul style="list-style-type: none"> • Improved plasma glucose after Cr • No urinary sugar detected after Cr • Improved insulin secretion in IVGTT after Cr • Serum Cr increased from undetectable to 1.2 ng/mL after Cr 	<ul style="list-style-type: none"> • Patient remained on Cr infusion thereafter (200 µg / 2 weeks), with no symptoms of glucose intolerance • Diagnosed Se deficiency treated with Se infusion given (100 µg for 99 d, 200 µg for 53 d) prior to Cr treatment
Verhage et al. (1996); case report	40 yo male with Crohn's disease; multiple bowel resections	IV CrCl ₃ with TPN (250 µg/d for 2 weeks), initiated 5 months after onset of symptoms	<ul style="list-style-type: none"> • TPN, unspecified duration (max 11 y?), last 6 months receiving ~ 15 µg Cr as TPN contaminant • Requires insulin (unspecified dose) • On prednisone for the last 10 y 	<ul style="list-style-type: none"> • Improved fractional rate of glucose clearance in IVGTT after Cr • Increased serum Cr after Cr treatment 	Patient had high-output jejunostomy

¹ dose of chromium treatment given in elemental Cr

4.2.3 Extracted data

Data were extracted from the included articles as presented in Table 5 (sourced from Balk et al. 2007). Authors of papers were not contacted for further information.

4.2.4 Quality assessment (individual studies)

All five of the included studies were case reports, which lacked adequate objectives and hypotheses. While case reports/series can provide new or rare observations that generate hypotheses, the evidence provided from these study designs are often regarded to be of poor quality in determining causal relationship and the effects of specific interventions (*NHMRC additional levels of evidence and grades for recommendations for developers of guidelines Introduction* 2009). The limitations of case reports/series are inherent to the study design; for example, publication bias is often noted as a limiting factor in these studies, exemplified by the observation that less than 10% of case reports/series describing treatment failures (Nissen and Wynn 2014).

In addition, given the uncontrolled nature of case studies, it is difficult to delineate the causal effect of chromium on glycaemic control. Within the included studies, multiple treatments were often given to the participants, which have the potential to confound the effects of chromium. For instance, variable rates of glucose and insulin infusion rates during chromium intervention period will have an impact on the systemic blood glucose levels measured (Brown et al. 1986). Other nutritional deficiencies were also identified and treated around the time when chromium infusions were given to patients (Brown et al. 1986; Tsuda et al. 1998), thereby the effects on blood glucose levels cannot be attributed solely to chromium. These major confounding factors on measures of blood glucose levels were not adjusted or controlled for in the included studies, thereby posing serious risk of biases.

4.2.5 Outcome data

A meta-analysis of the outcome data was deemed inappropriate given the variations in the outcome measurements; hence, a qualitative synthesis of the outcomes was completed for this review question.

Five case reports described the relationship between chromium and glucose levels in patients on long term TPN. In the first case report of chromium deficiency, Jeejeebhoy et al. (Jeejeebhoy et al. 1977) described a patient who had been receiving TPN for the last five years as a result of mesenteric thrombosis and complete enterectomy. The symptoms of weight loss and glucose intolerance were treated initially by the infusion of insulin. The study authors found that the patient had low blood and hair chromium levels and negative chromium balance. Infusion of chromium chloride (250 µg chromium/day) was given in the patient's TPN for 2 weeks, where positive chromium balance was achieved. After chromium treatment, the fractional rate of glucose clearance following an intravenous glucose tolerance test (IVGTT) improved to within the normal range, and exogenous insulin infusion was no longer required. Thereafter, the patient was maintained on 25 µg chromium/d given in TPN with normal glycaemic control and no adverse effects reported.

In a similar case, Freund et al. described a 45 year old female who presented with extensive weight loss and glucose intolerance 8 months after initiation of TPN (Freund et al. 1979). Her blood glucose levels peaked at 78 mmol/L, which was treated with 20 U/d insulin infusions. The chromium concentration in serum was 0.5 µg/dL (normal range given 0.5-9.0 µg/dL). Chromium chloride supplementation in TPN was given at a dose of 150 µg/d for 16 days. Within a few days of chromium treatment, euglycaemia was achieved without exogenous

insulin. In the latter stages of chromium treatment, insulin infusion was reintroduced. Shortly after chromium treatment, the patient died of overwhelming sepsis as a result of surgery.

Brown et al. reported 'chromium deficiency' in a patient on long term TPN as a result of multiple small bowel resections (Brown et al. 1986). After 7 months of TPN, the patient showed signs of glucose intolerance with hyperglycaemia and glycosuria. Insulin (10-30 U/d) was given with TPN to achieve euglycaemia. The plasma chromium concentration was low (0.1 µg/dL; normal reference 1.8-3.8 µg/dL) and chromium chloride (200 µg/d) was added to TPN for 14 days thereafter. During the period of treatment with chromium, the rate of glucose infusion decreased from 35 g/hr to 28 g/hr, with fluctuating rates of insulin given. After chromium treatment, serum glucose levels returned to within the normal range with no detectable glucose in urine and nil exogenous insulin required. Plasma chromium level remained unchanged after chromium supplementation. Supplemental zinc was given in TPN solution to achieve normal levels of serum zinc; the exact dose and timing of supplemental zinc were not reported. Upon hospital discharge, the patient was maintained on TPN containing 32 µg/d of chromium. At one year follow-up, no signs of glucose intolerance or chromium deficiency were detected.

Verhage et al. report on a 40 year old male on home TPN as a result of multiple bowel resections and Crohn's disease presented with signs of glucose intolerance (Verhage et al. 1996), requiring exogenous insulin. The level of contaminant chromium provided in home TPN solution was estimated to be 15 µg/d. In-hospital investigations found that the patient had reduced fractional glucose clearance rate in IVGTT and a serum chromium level of 0.084 µmol/L. The composition of nutrients in TPN was changed during the hospital stay, with increased intakes of chromium and zinc. After the addition of chromium chloride in TPN (250 µg/d for 2 weeks), fractional glucose clearance in IVGTT returned to within the normal range, coinciding with a higher level of serum chromium (1.7 µmol/L).

Tsuda et al. described a male patient on long term TPN as a result of intestinal pseudo-obstruction (Tsuda et al. 1998). After 13 years of maintenance on TPN, the patient was treated for selenium deficiency before hyperglycaemia and glycosuria were noted. Serum chromium concentrations were undetectable so chromium infusion (200 µg/d) was administered for 2 weeks. After chromium treatment, plasma glucose levels were within the normal range and urinary sugar was undetectable. IVGTT revealed no changes in glucose levels, however, there was an improvement in insulin secretion following the intravenous bolus of glucose. The patient was maintained on TPN containing 14 µg/d chromium with no signs of glucose intolerance for 2 months post-treatment.

4.2.6 Characteristics of interventions

The differences in the routes of chromium administration should be considered in the interpretation of this review. All of the identified studies were case reports of patients who were administered chromium as part of their TPN (Brown et al. 1986; Freund et al. 1979; Jeejeebhoy et al. 1977; Tsuda et al. 1998; Verhage et al. 1996). The dose of IV chromium treatment ranged from 150-250 µg/d, administered over a period of 14-16 days. IV delivery of nutrients bypasses the factors that influence nutrient bioavailability and uptake in the gastrointestinal tract, thereby ensuring 100% of the dose will be delivered to the systemic circulation instantaneously. This is particularly relevant for chromium treatment as the estimated enteral absorption of chromium into the systemic circulation is estimated to be 0.4-2.5% of the ingested dose (Institute of Medicine 2001). To replicate the systemic concentration of IV administered chromium of 250 µg, the oral intake of chromium would need to be 500-fold higher than the current estimated mean chromium intake in Australian adults (20-36 µg/d) (Food Standards Australia New Zealand 2008). The potential adverse effects of high intakes of chromium are currently unknown, especially without an established Upper Level of chromium intake.

4.2.7 Characteristics of participants

In addition to the heterogeneity in age and sex of included participants, the majority of the study participants in the current review presented with complex underlying medical conditions and complications for example mesenteric thrombosis, Crohn's disease. The critical condition of the included participants is highlighted in the subsequent death of one reported case (Freund et al. 1979).

While all included papers report chromium biomarkers at baseline, the usefulness of chromium measures to reflect chromium status has not been proven. For instance, serum chromium, the most common chromium measure, did not change in 2 out of the 5 included cases despite daily IV chromium supplementation over periods that exceed 2 weeks (Brown et al. 1986; Freund et al. 1979). Furthermore, no data on chromium biomarkers within the population were available for comparison and therefore the interpretation of chromium status by the reported biomarkers is unclear.

4.3 Summary of new evidence

While the five included case reports of patients dependent on TPN showed favourable improvements in blood glucose levels, the confounding factors inherent to the cases cast serious doubts over the reported results. Patients were often given changing rates of glucose and/or insulin infusion to maintain euglycaemia thereby confounding the effects of chromium treatment (Brown et al. 1986). Furthermore, two of the case reports described other nutritional deficiencies, such as zinc and selenium, which were treated with supplementation prior to or concurrent with chromium treatment (Brown et al. 1986; Tsuda et al. 1998). Potential adverse effects of chromium treatment in this population were not reported. Although one patient died of overwhelming sepsis shortly after chromium treatment, the study authors' did not attribute chromium to the cause of death (Freund et al. 1979).

5 'Chromium Deficient' Population – Weight of evidence

5.1 Degree of certainty

5.1.1 Study biases

The body of evidence available poses a high risk of bias, especially with the lack of an appropriate control group (in case reports) and failure to adequately control confounding factors.

A number of confounding factors of the included studies should be considered in the current review. Patients with long term TPN requirements were often given varying rates of glucose and/or insulin infusion to maintain euglycaemia, which confounds the effects of chromium treatment. For example in the case report described by Brown et al. a reduced rate of glucose infusion was given during and after chromium intervention, and this could explain the favourable effect observed in serum glucose levels (Brown et al. 1986). Furthermore, two of the case reports described other nutritional deficiencies, such as zinc and selenium, which were treated with supplementation prior to, or concurrent with, chromium treatment (Brown et al. 1986; Tsuda et al. 1998). Current evidence suggests that zinc supplementation can improve glycaemic control in healthy populations and patients with chronic metabolic diseases (Capdor et al. 2013). The simultaneous treatment of nutrient deficiencies implies that the results cannot be attributed to the administration of chromium with any certainty.

5.1.2 Indirectness

All of the included studies used IV chromium infusion as the intervention. The indirectness in the route of administration in chromium treatment is such that it is difficult to replicate chromium intake in foods.

Furthermore, the fasting blood glucose levels of patients on long term TPN are difficult to determine as food components are administered intravenously. Whether blood glucose fluctuations and exogenous insulin requirements in long term TPN patients are reflective of the effects of chromium on blood glucose levels remain unclear.

5.1.3 Imprecision and inconsistency

As meta-analysis was not completed for this review, imprecision and inconsistency of the results could not be assessed.

5.1.4 Other methodological issues

Other methodological issues in the present review include the measurement of chromium status and possibility of publication bias. While all studies reported one or more biomarkers of chromium, the relevance of the reported results in relation to the normal range is unclear in all cases. The lack of reported chromium status in the study population also complicates the identification of chromium deficiency in this population (as discussed in section 4.2.7). In this systematic review, the review authors have included the reports of 'chromium deficiency' in the population group that is likely to exhibit true deficiency and have not relied on the study authors' description of 'chromium deficient' population.

The possibility of publication bias in this body of evidence is considered large, considering the designs of included studies. Case reports and case series are more often reported if the case had positive outcome with treatment, while those with negative outcomes may not be reported or published (as discussed in section 4.2.4).

5.2 Assessment of body of evidence

5.2.1 Consistency and causality of relationship

Causality of the relationship is not established. All included studies lacked an appropriate control group, presenting a serious concern for risks of bias in the studies. Furthermore, the case reports often present many confounding factors, including changing rates of glucose and insulin infusion during or following chromium treatment, and supplementation of other nutrients. Therefore, under multiple confounding factors, the true effect of chromium on blood glucose levels cannot be determined.

The indirectness in measurement interpretation and route of chromium administration should also be considered in the assessment of the current body of evidence. To replicate the intravenously administered doses of chromium in the included studies, oral chromium intake of approximately 500-fold of the current Australian and New Zealand chromium intake is required. Furthermore, the blood glucose levels of patients receiving long term TPN are unlikely to be reflective of populations that are consuming food.

5.2.2 Plausibility

Chromium has been suggested to improve insulin sensitivity by promoting the insulin signalling pathway in peripheral tissues. *In vitro* studies suggest that the primary mechanism of action originates from the interaction between chromium and proteins involved in the

insulin signalling pathway (Miranda and Dey 2004). In patients receiving long term TPN (described above), the identification of 'chromium deficiency' and concomitant signs of glucose intolerance formed the basis of the beneficial effect of chromium on optimal glucose metabolism. In humans, multiple hypotheses regarding how chromium acts on insulin sensitivity have been proposed (Stearns 2007), with little consensus present in the literature. The current collection of included studies offered little support for the biological plausibility of chromium action on glucose metabolism in the chromium deficient population. Therefore, the biological plausibility of chromium affecting blood glucose levels is uncertain.

5.2.3 Summary of the body of evidence

The small number of studies limits the evidence for the relationship between chromium and blood glucose levels in the 'chromium deficient' population. The included studies present with serious concerns for the validity of results due to the lack of a control group and failure to adequately control for confounding factors, such as co-administration of other nutrients or insulin.

Furthermore, the studies were conducted in populations that had complicated medical conditions, which does not represent the Australian and New Zealand general populations. All included studies also used IV route of administration for chromium treatment, which is not applicable for extrapolation of the relationship to chromium intake in food.

For a food-health relationship to be substantiated there has to be a consistency of effect across high quality studies, with known biological plausibility and proven causality of effect. Given the indirectness of both sample population and method of chromium administration, the review authors consider that, based on the current evidence, the relationship between chromium and blood glucose concentrations in the chromium deficient population is not able to be assessed.

5.3 Applicability to Australia and New Zealand

5.3.1 Intake required for effect

As the effect of chromium on blood glucose levels in the 'chromium deficient' population cannot be assessed, the intake required for effect could not be established. However, it is worth noting that all of the included studies administered chromium via IV infusions. Chromium given intravenously bypasses the limiting step of absorption in the gastrointestinal tract and hence the results from IV chromium interventions are not appropriate to determine the dietary intake required for effect.

5.3.2 Target population

All included studies were conducted in patients with complicated medical conditions, requiring long term TPN. All included patients were adults.

5.3.3 Extrapolation from supplements

As the effect of chromium on blood glucose levels could not be assessed in the 'chromium deficient' population, extrapolation from supplements was not applicable.

6 ‘Chromium Deficient’ population – Conclusion

Based on the current body of evidence and the limitations discussed, including IV administered chromium, medical complications in the study participants, numerous confounding issues and serious risk of study biases, it was not possible to assess the relationship between chromium intake and blood glucose concentrations in the ‘chromium deficient’ population.

7 Free-Living Population – Evaluation of new evidence

The aim of the current review was to update the existing evidence base on whether dietary chromium intake affects blood glucose levels in populations consuming a wide range of foods (free-living population). Therefore, an updated literature search was conducted as described in the Balk et al. review, covering the period of January 2006 to July 2015.

7.1 Methods

7.1.1 Search strategy

MEDLINE and Commonwealth Agricultural Bureau were searched for original research papers published from January 2006 to 17th July 2015, limited to human investigations and English language publications. Search terms used were “chromium,” “diabetes mellitus,” “glycaemia,” glycosylated haemoglobin,” “metabolic syndrome,” and “insulin resistance.” Relevant MeSH headings were used in search databases. The full search strategy is described in Appendix 1. Table 8 describes the PICOTS inclusion criteria for the screening of citations¹. For the purpose of this review, trials that included only chromium supplementation, that is without other treatments, are included in the selection of studies. Hand searching for other relevant studies was conducted through reference lists of included studies.

Table 8: PICOTS criteria for studies of chromium supplementation in the free-living population as per Balk et al. (2007)

Population	Humans (normoglycaemic, glucose intolerant or diabetes mellitus), n ≥ 10 receiving chromium
Intervention	Chromium supplementation (any formulation)
Comparator	Placebo
Outcome	Glycaemic control (fasting blood glucose, insulin, OGTT, HbA1c)
Time	Supplement duration ≥ 3 weeks
Study design	Randomised Controlled Trials

7.1.2 Investigators

Two investigators independently screened the search output for potential studies as per the predefined inclusion criteria described.

¹Participants with diabetes were included for the purposes of the updated literature review, but were subsequently excluded from the meta-analysis. It is not clear that results in people with diabetes can be extrapolated to people without diabetes. The existing review of Balk et al. (2007) found a relationship in people with diabetes. There was no relationship in those without diabetes and this was a non-effect, not a relationship that was not statistically significant (Table 5). As the lack of effect in those without diabetes was direct evidence based on a substantial quantity of data, it would not be overturned by indirect evidence extrapolated by updating the review in those with diabetes.

7.1.3 Data extraction and statistical analysis

Balk et al. defined normoglycaemic to be fasting blood glucose levels below 5.6 mmol/L as per the WHO or the ADA criteria. Glucose intolerant participants were considered as those that either had impaired fasting glucose (fasting plasma glucose 5.6–7.0 mmol/L) or impaired glucose tolerance (2-h post-load glucose concentration 7.8–11.1 mmol/L). We have defined the categories of glycaemic control as per Diabetes Australia criteria, with normoglycaemic defined as fasting blood glucose < 5.5 mmol/L and glucose intolerance as either impaired fasting glucose (fasting blood glucose 5.5–6.9 mmol/L) or impaired glucose tolerance (fasting blood glucose < 7 mmol/L) (Diabetes Australia 2014). Despite the slight variations in the cut offs applied for the different categories of glycaemic control, misclassification of populations is unlikely. For a mixed cohort of normoglycaemic and impaired glucose tolerance populations, the majority of population determines whether the population is classified as normoglycaemic or glucose intolerant.

Fasting blood glucose data from individual studies in Balk et al.'s review were extracted from digitised graphs (Figure 2 in Balk et al.'s paper (Balk et al. 2007)) using WebPlotDigitizer (<http://arohatgi.info/WebPlotDigitizer/app/>). Individual data points with no available standard error were not extracted for meta-analysis, as per Balk et al.'s statistical analysis. Individual study data from Balk et al.'s review were required to assess statistical heterogeneity and for generating a funnel plot as an assessment of potential bias. Where digitised graphical data did not match the overall summary statistics, numerical values from subgroup analysis were used to update the meta-analysis.

Mean between-group differences and the corresponding 95% CI of fasting blood glucose were used to generate random effects meta-analysis models using the generic inverse variance method in STATA 13.0 (StataCorp 2013).

7.2 Results

7.2.1 Search results

The PRISMA flow chart details the number of studies screened and included in the review (Figure 2). Appendix 3 describes the 21 studies excluded at full-text screening with reasons for exclusion.

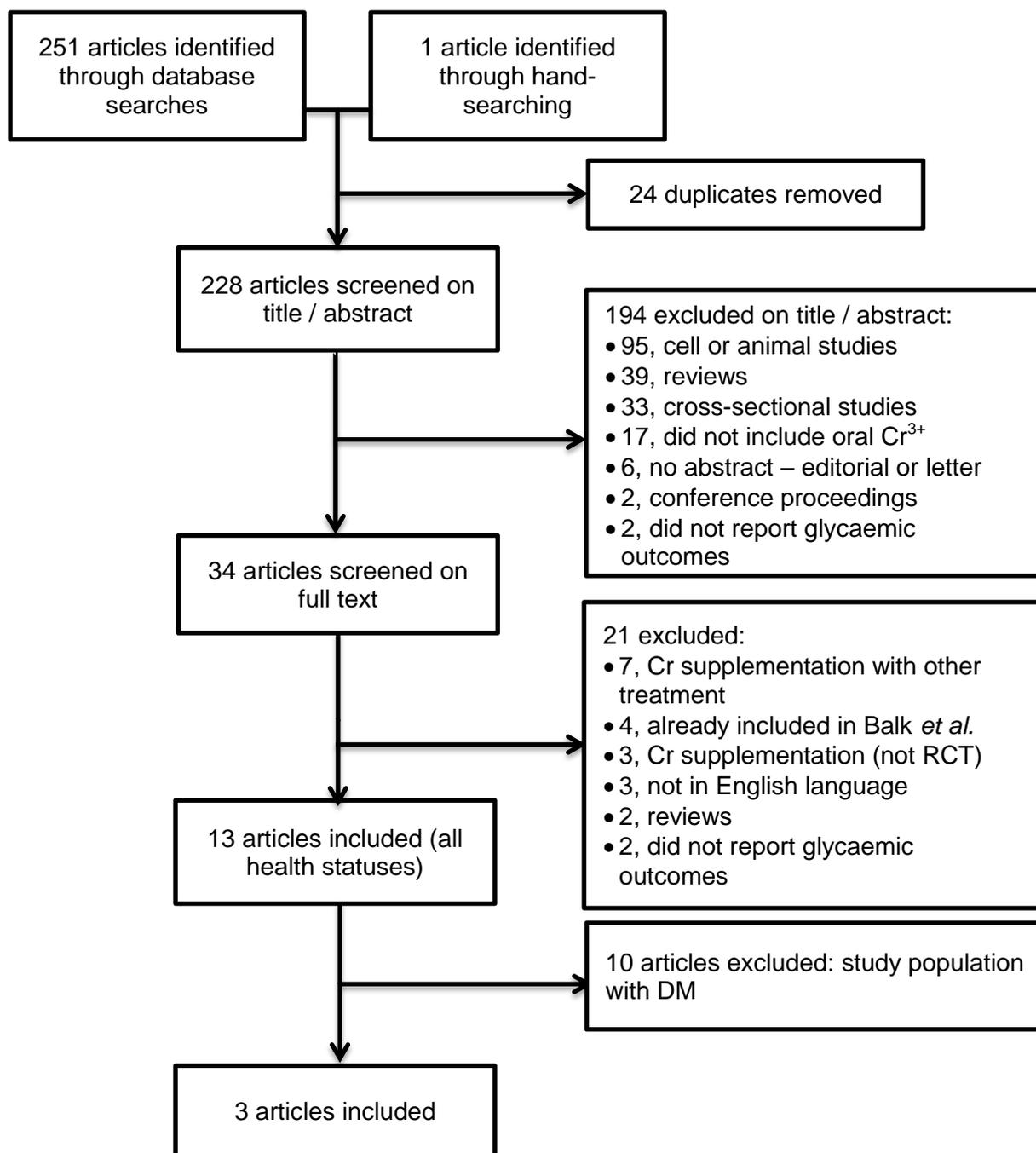


Figure 2. PRISMA flow chart describing the systematic review process for the free-living population

7.2.2 Included studies

Thirteen studies were identified which satisfied the inclusion criteria that were published since Balk et al.'s 2007 review. Ten papers described a study population with DM (Cefalu et al. 2010; Chen et al. 2014; Guimarães et al. 2013; Jain et al. 2012; Kleefstra et al. 2007; Król et al. 2011; Lai 2008; Rocha et al. 2014; Sharma et al. 2011; Wang et al. 2007), which FSANZ determined to be out of the scope for this review in the Free-Living population. The three remaining papers (Ali et al. 2011; Iqbal et al. 2009; Kim et al. 2011), including normoglycaemic and impaired glucose tolerance population, were included for data extraction and meta-analysis. Information that was extracted from the three included studies is shown in Table 9.

One of the included studies was conducted in participants with impaired glucose tolerance, impaired fasting glucose or metabolic syndrome (Ali et al. 2011). In a randomised, double-blind, modified cross-over study, participants were randomised into one of two chromium supplementation doses (500 or 1000 µg chromium picolinate) and then were randomised further for the order of placebo or active supplementation. No significant effects were reported for fasting blood glucose or HbA1c as a result of chromium supplementation at either of the two doses (Table 9).

Another of the included studies involved participants with metabolic syndrome. The study was conducted to determine the effect of chromium treatment on insulin sensitivity and glucose outcomes in a double-blind, placebo-controlled RCT (Iqbal et al. 2009). Investigators recruited 63 participants with metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III. The participants were treated with 1000 µg chromium picolinate (124 µg elemental chromium) or placebo for 16 weeks. Participants were heterogeneous in terms of their level of insulin sensitivity (52% of participants had either impaired fasting glucose or impaired glucose tolerance) at baseline. No significant effects were reported for fasting glucose levels (Table 9).

The other included study described chromium treatment (400 µg chromium chloride; 131 µg elemental chromium) in overweight Korean children for 6 weeks. Enrolled children were randomised into treatment or placebo stratified by age, sex and Body Mass Index (BMI). All participants attended a lifestyle program for weight management concurrently with chromium treatment or placebo. No significant effect of chromium treatment was observed on fasting blood glucose (Table 9).

Table 9: Study details of the three included studies

Reference	Ali et al. (2011).
Study design	RCT, modified cross-over, 6 months, double-blind
Objectives	To investigate the effects of daily chromium picolinate supplementation on serum measures of glucose tolerance and insulin sensitivity in patients at high risk for Type 2 DM
Sample size	59 enrolled, randomised into either 500 µg or 1000 µg of chromium picolinate, 56 completed; sample size calculation assumed 9.5% difference between the 500 µg and 1000 µg groups.
Participants	Participants with impaired glucose tolerance, impaired fasting glucose or metabolic syndrome, mean age 56.9 ± 12.1 y, 36% males
Interventions	Participants completed two 6 month sequences of intervention (500 µg or 1000 µg chromium picolinate/d as a single dose) and placebo. Unclear whether the doses reported were elemental or as a complex. No wash-over period between placebo and treatment.
Methods	Methods for glucose and HbA1c determination were not stated.
Confounders	Controlled by cross-over design, however, no wash out period between intervention and placebo. Statistical analyses unclear as to whether the change values were calculated at baseline prior to any treatment/placebo or immediately between the treatment/placebo phases.
Results	<p>Mean change in fasting blood glucose for 500 µg chromium picolinate treatment phase was -0.06 mmol/L (95% CI: -0.22, 0.11); change in fasting blood glucose in the corresponding placebo phase was -0.16 mmol/L (95% CI: -0.32, 0.01). Mean change in fasting blood glucose for 1000 µg chromium picolinate treatment phase was -0.02 mmol/L (95% CI: -0.21, 0.17), change in fasting blood glucose in the corresponding placebo phase was -0.03 mmol/L (95% CI: -0.22, 0.17). Whole blood HbA1c change for the 500 µg chromium picolinate treatment phase was 0.1% (95% CI: 0, 0.2); change in corresponding placebo phase was 0.1% (95% CI: 0, 0.2). In the 1000 µg chromium picolinate phase, the change in HbA1c was 0% (95% CI: -0.1, 0.1); change in HbA1c in the corresponding placebo phase was 0.1% (95% CI: 0, 0.2).</p> <p>Mean difference between phases for the 500 µg chromium picolinate group: fasting blood glucose, 0.1 mmol/L (95% CI: -0.13, 0.33); HbA1c, 0% (95% CI: -0.14, 0.14)</p> <p>Mean difference between phases for 1000 µg chromium picolinate group: fasting blood</p>

	glucose, 0.01 mmol/L (95% CI: -0.26, 0.28), HbA1c, -0.1% (95% CI: -0.24, 0.04)
Notes	No adverse effects were noted.
Funding sources	NIH, CDC. Active and placebo capsules provided by Nutrition 21, a producer of chromium picolinate supplements.

Reference	Iqbal et al. (2009)
Study design	RCT, double-blind, placebo-controlled
Objectives	To determine the effects of chromium picolinate on glucose metabolism in patients with metabolic syndrome
Sample size	63 enrolled, 60 completed; sample size was calculated for estimated change in insulin sensitivity
Participants	Participants with National Cholesterol Education Program Adult Treatment Panel III-defined metabolic syndrome, age between 18 and 75, 49% males, 52% of participants had impaired glucose metabolism.
Interventions	Participants were randomised into chromium picolinate (1000 µg chromium picolinate/day; 124 µg elemental chromium) and placebo groups for 16 weeks.
Methods	Plasma glucose was analysed by an enzymatic calorimetric assay.
Confounders	Participants were heterogeneous in terms of their level of insulin sensitivity (52% of participants had impaired glucose metabolism (either IFG or IGT) at baseline).
Results	Change in fasting glucose concentration was not statistically significant in the chromium picolinate group (4.66 ± 0.81 to 4.92 ± 0.91 mmol/L (mean \pm SD), $P = 0.09$). Fasting glucose concentration was also unchanged in placebo group (4.54 ± 0.64 to 4.5 ± 0.85 mmol/L, $P = 0.89$).
Notes	Investigators measured urinary chromium excretion.
Funding sources	Supported by grants from Translational Research Centre. Active and placebo capsules provided by Nutrition 21, a producer of chromium picolinate supplements.

Reference	Kim et al. (2011)
Study design	RCT, parallel, double-blind
Objectives	To examine the beneficial effects of chromium supplementation on insulin sensitivity and body composition in overweight children simultaneously modifying lifestyle
Sample size	31 enrolled, 25 completed; no sample size calculation given
Participants	Children aged 9-12 y, overweight, 48% male
Interventions	Participants were randomised into chromium chloride supplementation (131 µg elemental chromium/d as a single dose) or placebo for 6 weeks. All participants participated in lifestyle management program including aerobic exercise and diet education for the duration of supplementation period.
Methods	Fasting plasma glucose was measured enzymatically using an ADVIA 1650 apparatus.
Confounders	The effects of chromium may be modulated by pubertal status of children; authors explored the modulation of pubertal status in secondary analyses. All participants were involved in lifestyle program for weight management during supplementation period.
Results	Change in fasting blood glucose in chromium supplementation group was -0.38 ± 0.64 mmol/L (mean \pm SEM). Change in fasting blood glucose in placebo group was 0.15 ± 0.37 mmol/L. The effect of chromium on fasting blood glucose was not statistical significance as determined by Mann-Whitney U test ($P = 0.2$).
Notes	No adverse effects were reported.
Funding source	Funding from non-industry source.

7.2.3 Extracted data

Data were extracted as reported in the papers; authors of papers were not contacted. Fasting blood glucose data from newly included studies were extracted numerically. Where fasting glucose levels were given in mg/dL, data were converted to mmol/L by the following formula:

$$\text{glucose (mmol/L)} = (\text{glucose [mg/dL]} \div 180.1559) \times 10$$

Where within-group changes in fasting blood glucose were provided numerically, the data were extracted to calculate mean differences of between-group changes in fasting blood glucose. Before and final values of fasting blood glucose and the corresponding P-values for two-tailed T-tests were used to provide mean change values for treatment and placebo groups by calculating the difference between final and initial fasting blood glucose concentration. T-values were obtained by the formula:

$$[\text{inv}(P\text{-value, degrees of freedom})]$$

Standard error of the within-group change in fasting glucose was calculated by:

$$[\text{SE} = \text{mean difference} \div t\text{-value}]$$

Mean between-group differences of fasting blood glucose were calculated by:

[mean difference of change between groups = mean change of treatment group – mean change of placebo group].

Standard error of the mean between-group difference of fasting blood glucose were calculated by:

$$[\text{SE} = \sqrt{((\text{SD}_{\text{treatment}}^2 / n_{\text{treatment}}) + (\text{SD}_{\text{placebo}}^2 / n_{\text{placebo}}))}]$$

95% CI of mean between-group differences of fasting blood glucose were calculated by:

$$[\text{LCI} = \text{mean} - (\text{SE} \times 1.96); \text{UCI} = \text{mean} + (\text{SE} \times 1.96)]$$

7.2.4 Quality assessment (individual studies)

Studies included in Balk et al.'s review were assessed for potential risk of biases by Balk et al. and therefore were not assessed again in this review. The newly included studies were assessed for potential risk of biases using the Cochrane risk of bias tool, as per recommendation from the GRADE process (Guyatt et al. 2011).

Ali et al.'s paper (Ali et al. 2011) describes a double-blind, modified cross-over, RCT involving 59 participants with impaired glucose tolerance given chromium supplementation (at either 500 or 1000 µg chromium picolinate/d) and placebo for 6 months. The aim of this study was to determine the effects of daily chromium picolinate supplementation on serum measures of glucose tolerance and insulin sensitivity in patients at high risk for Type 2 DM. Assessment of risk of biases for this study are described in Table 10. The methods of random sequence generation and allocation were not described clearly in the report and therefore have been judged to present unclear risk of bias. Dietary intake of participants was not assessed. The duration of supplementation was longer than most studies identified in Balk et al.'s systematic review and therefore should be sufficient to demonstrate the proposed health effect.

Iqbal et al. reported on a double-blind, placebo-controlled RCT in participants with metabolic syndrome ($n = 63$) and involved randomisation of participants into chromium treatment (124 μg elemental chromium) or placebo for 16 weeks. The aim of this study was to determine the effects of chromium picolinate on glucose metabolism in patients with metabolic syndrome. No dietary data for the participants were presented. The methods of random sequence generation and allocation concealment were not clearly described in the paper and hence posed an unclear risk of bias (Table 10). The study authors completed a 'modified intention-to-treat' analysis where data were excluded due to incomplete or outlying variables ($n = 6$ excluded); it is unclear to us as to whether the exclusion of data poses a risk of attrition bias.

The RCT by Kim et al. (2011) was a parallel, double-blind chromium supplementation (400 μg of chromium chloride for 6 weeks) in overweight children. The aim of this study was to examine the effects of chromium supplementation while simultaneously modifying lifestyle factors, on insulin sensitivity and body composition in overweight children. The methods of randomisation and allocation of concealment were not described clearly in the report and therefore have been judged to present unclear risk of bias (Table 10). The background diets were not described, and the participants were engaging in a lifestyle weight management program, including aerobic exercise (twice/week) and diet education to achieve a "balanced low-calorie diet." It is unclear whether an intervention period of 6 weeks is sufficient to demonstrate the proposed health effects of chromium.

Table 10: Risk of bias assessment of included studies

Ali et al. (2011)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Quote: "this study was a randomised... trial"
Allocation concealment (selection bias)	Unclear	Method of concealment not clearly described. Quote: "supplying pharmacy personnel encoded the treatment supplements and matching placebos"
Blinding of participants and personnel (performance bias)	Low	Blinding of participants and key study personnel stated. Intervention and placebo capsules were similar in shape, size and appearance and indistinguishable.
Blinding of outcome assessment (detection bias)	Low	No blinding of outcome assessment. The outcome measurement is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low	Intention-to-treat analysis, with missing data imputed appropriately.
Selective reporting (reporting bias)	Low	No study protocol, but the report included all expected outcomes as per study aim.
Other bias	Low	Nutrition 21, a producer of chromium picolinate, provided active and placebo capsules.

Iqbal et al. (2009)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Quote: "Subjects... randomised in a 1:1 double-blind fashion to receive either CrPic or matching placebo." The method of randomisation was not described.
Allocation concealment (selection bias)	Unclear	Method of concealment was not described.
Blinding of participants and personnel (performance bias)	Low	Blinding of participants and key study personnel stated. Intervention and placebo capsules were matched in appearance.
Blinding of outcome assessment (detection bias)	Low	No blinding of outcome assessment. The outcome measurement is not likely to be influenced by lack of binding.
Incomplete outcome data (attrition bias)	Unclear	"Modified Intention-to-treat analysis;" study authors excluded data due to incomplete or outlying data ($n = 6$ excluded).
Selective reporting (reporting bias)	Low	No study protocol, but the report included all expected outcomes as per study aim.
Other bias	Low	Nutrition 21, a producer of chromium picolinate, provided active and placebo capsules.

Kim et al. (2011)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	The method of randomisation was not described.
Allocation concealment (selection bias)	Unclear	The method of concealment was not described.
Blinding of participants and personnel (performance bias)	Low	Quote: "the participants and investigators were blinded to randomisation"
Blinding of outcome assessment (detection bias)	Low	No blinding of outcome assessment. The outcome measurement is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Unclear	Intention-to-treat analysis not carried out. Insufficient information about missing data. Data from dropouts not included in the analysis.
Selective reporting (reporting bias)	Low	No study protocol, but the report included all expected outcomes as per study aim.
Other bias	Low	Funding from a non-industry source.

7.2.5 Outcome data

The included study by Kim et al. (2011) examined the effect of chromium on fasting blood glucose in normoglycaemic overweight children. As all the other included studies within Balk et al.'s meta-analysis of normoglycaemic populations were in adults, we did not deem it to be appropriate to update the overall analysis to include Kim et al.'s study in children. Instead, a subgroup analysis stratified by children and adults is presented in Figure 3. In the overall analysis, chromium supplementation produced a non-significant decrease of 0.04 mmol/L (95% CI -0.13, 0.05) in fasting blood glucose. The risk of publication bias in the normoglycaemic population appears to be low, as evidence by a largely symmetrical funnel plot (Figure 4).

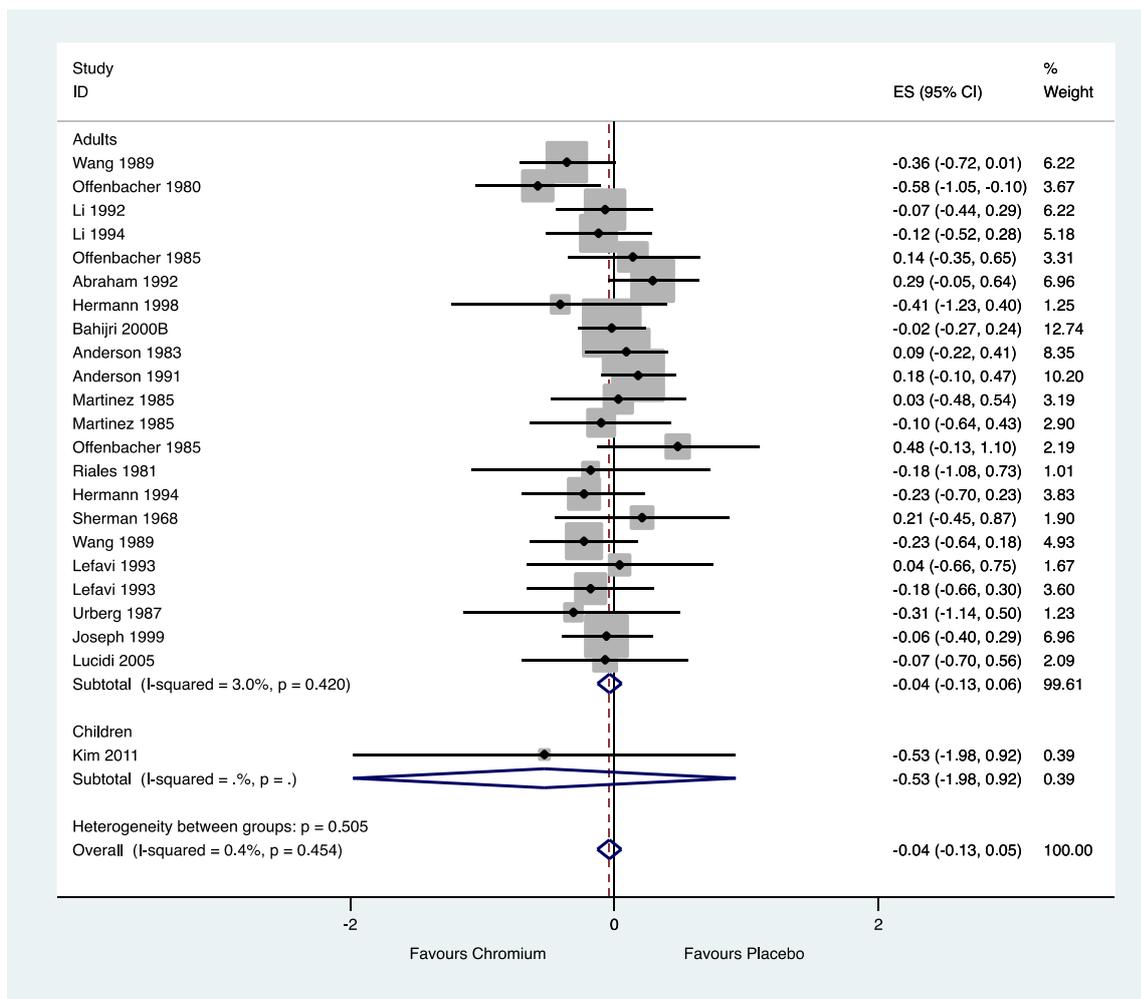


Figure 3. Forest plot showing the effect of chromium supplementation on fasting blood glucose in normoglycaemic population, stratified by adults/children. Strata were ordered as per Balk et al.'s forest plot with additional points added sequentially.

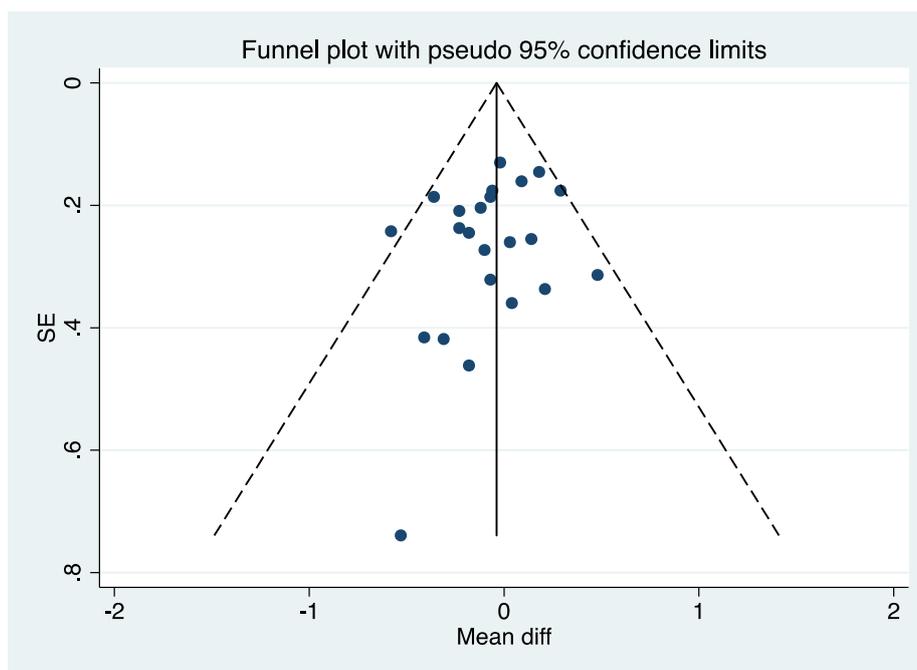


Figure 4. Funnel plot shows results from all included studies in normoglycaemic population.

In the glucose intolerant population, the results from studies by Ali et al. (Ali et al. 2011) and Iqbal et al. (Iqbal et al. 2009) were added to the meta-analysis of change in fasting blood glucose (Figure 5). The updated meta-analysis revealed that chromium supplementation produced a non-significant increase of 0.01 mmol/L in fasting blood glucose (95% CI -0.1, 0.13). The risk of publication bias in the population with glucose intolerance appears to be low, as evidenced by a largely symmetrical funnel plot (Figure 6).

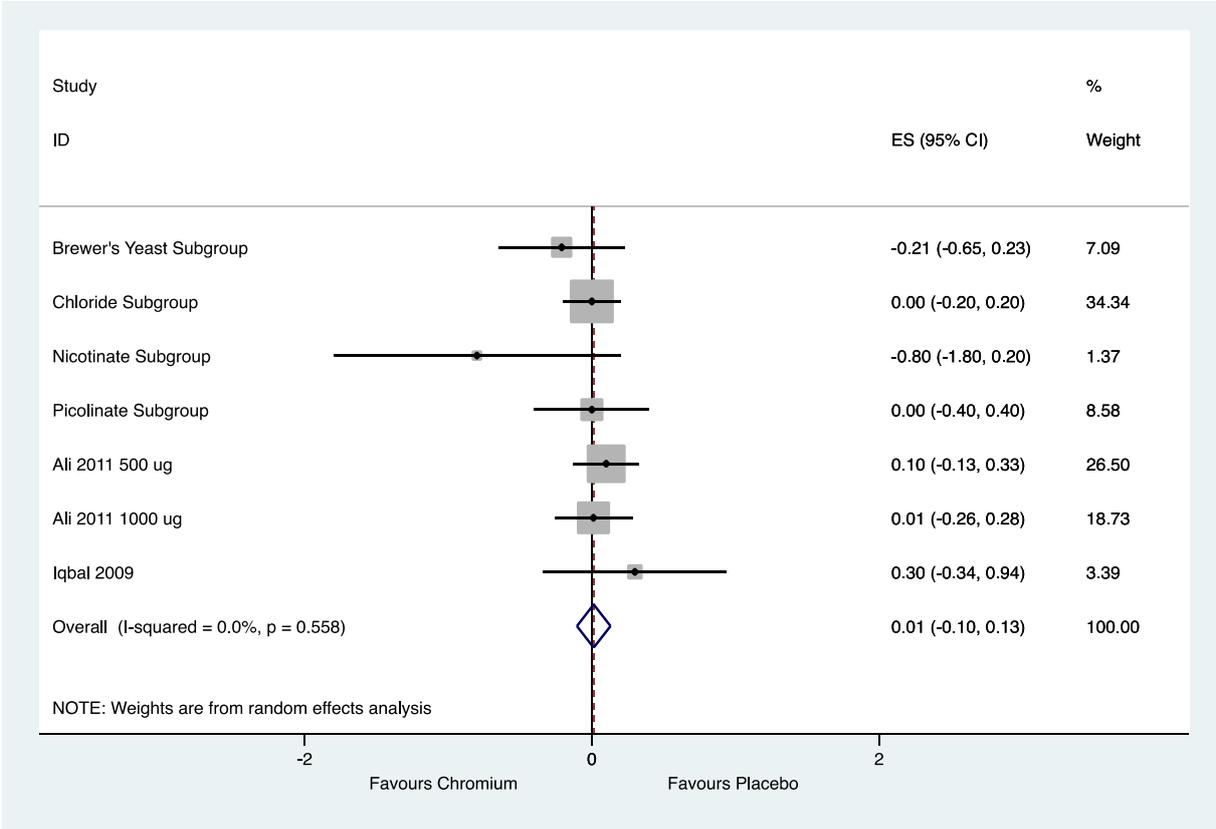


Figure 5. Forest plot showing the effect of chromium supplementation on fasting blood glucose in populations with glucose intolerance. Numerical data for subgroup were extracted from Balk et al. review (Online Supplementary File), with the three new strata added sequentially (Ali et al. 2011, Iqbal et al. 2009).

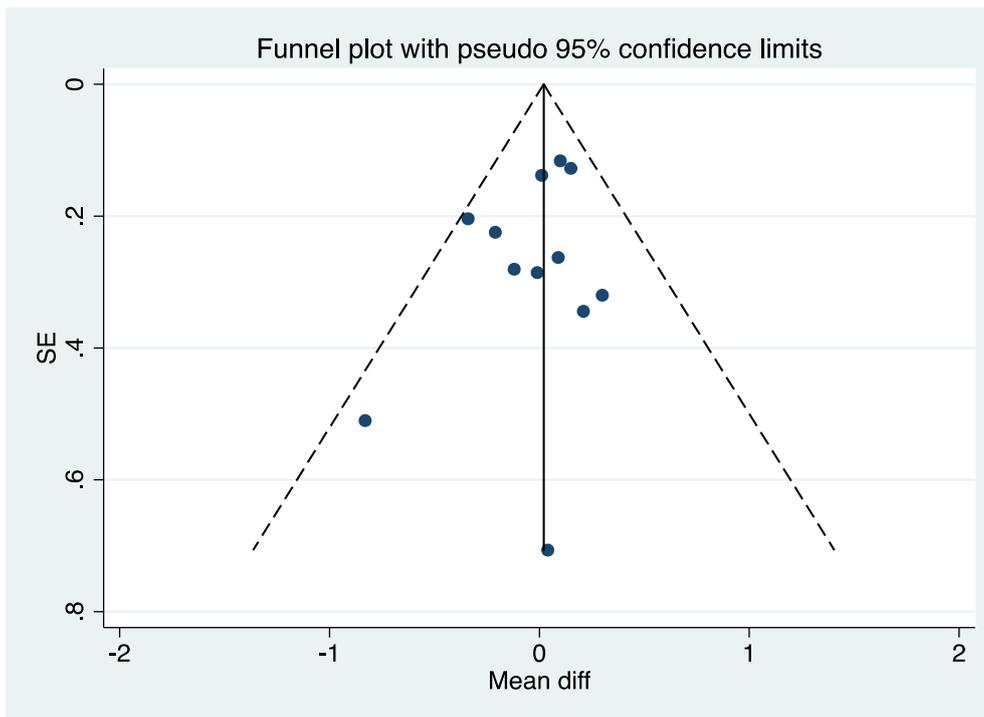


Figure 6. Funnel plot shows results from all included studies in populations with glucose intolerance.

7.3 Summary of new evidence

The updated search identified 252 potentially relevant articles, of which 13 met the inclusion criteria as per Balk et al.'s review. Ten out of the 13 identified studies were conducted in people with DM, which is out of the scope of the present systematic review. The three remaining studies, one in overweight normoglycaemic children (Kim et al. 2011) and two other studies conducted in participants with glucose intolerance or metabolic syndrome (Ali et al. 2011; Iqbal et al. 2009), provided new data to update Balk et al.'s original meta-analyses examining the effect of chromium supplementation on fasting blood glucose. The newly included studies did not change the overall results of Balk et al.'s analyses, that is no significant change in fasting blood glucose as a result of chromium supplementation in normoglycaemic or impaired glucose tolerance populations could be determined.

8 Free-Living Population - Weight of evidence

8.1 Degree of certainty

The degree of certainty in the food-health relationship is determined by the totality of the evidence as assessed by study biases, potential indirectness of the included studies, imprecision and inconsistency of the effect (as assessed by meta-analysis) and other methodological issues which may interfere with the degree of certainty in the relationship.

8.1.1 Normoglycaemic population

In the Balk et al. review, study biases of the comparisons within normoglycaemic population were assessed by the criteria defined in the National Kidney Foundation (National Kidney Foundation 2002). Twelve of the 19 studies from Balk et al.'s review were classified as moderate quality, which may have some deficiencies in study designs but none likely to cause major bias. The assessment of study biases in the additional study by Kim et al. (Kim

et al. 2011) was conducted using the Cochrane Collaboration's risk of bias tool. No serious risk of biases was identified in Kim et al.'s study (Table 10).

The included studies from Balk et al.'s review were conducted in adults with normal glucose concentrations; limited information regarding the included studies were available from Balk et al.'s review. The inclusion of participants with underlying subclinical conditions, such as hypertension, may introduce indirectness of population group in the assessment of the proposed relationship. The additional paper that was identified since the review by Balk et al. was carried out in overweight children with normal blood glucose (Kim et al., 2011), which further introduced the confounding factor of age into the present review.

Furthermore, a range of different forms of chromium (mostly chloride, but also included yeast, nicotinate, picotinate) and doses of chromium supplements (5-924 µg elemental chromium) were used, which complicates the assessment of the relationship. The additional study by Kim et al. (2011) used chromium chloride at 131 µg elemental chromium/d. The interaction between different forms of chromium and the effect on blood glucose levels was not assessed as part of this review.

The confidence interval of normoglycaemic adults as described by Balk et al. (Balk et al. 2007) was narrow and the addition of Kim et al.'s report in children (Kim et al. 2011) had no significant bearing on the overall estimated mean and confidence interval of the effect of chromium on fasting blood glucose. The precision of the relationship, as evidenced by the narrow confidence interval, excludes any clinically significant changes in fasting blood glucose as a result of chromium supplementation. However, the small sample size from the current review ($n = 322$) is such that it is difficult to dismiss the possibility for small differences of effect by chromium supplementation that are not detectable with the present sample size. Furthermore, the included studies often lacked power calculations to generate appropriate testing of the estimated effect of chromium supplementation.

In normoglycaemic adults, no serious inconsistency of results were observed ($I^2 = 3\%$, $P = 0.420$). The addition of the study in overweight children did not introduce significant statistical heterogeneity ($I^2 = 0.4\%$, $P = 0.454$).

While no serious concerns were found in the potential biases of included studies, indirectness of the included evidence, imprecision and inconsistency of the effect (as assessed by meta-analysis) and other methodological issues, the current review are limited by small sample size and other confounding factors within study populations. Therefore, the review authors deemed that there is a moderate degree of certainty that chromium has no effect on blood glucose levels in normoglycaemic adults. While only one study was identified in overweight children, the addition of this study did not alter the general relationship; therefore it may be assumed that the non-effect of chromium on blood glucose levels may also be applicable to normoglycaemic children.

8.1.2 Impaired glucose tolerance population

In the Balk et al. review (2007), study biases of the comparisons within impaired glucose tolerance populations were assessed by the criteria defined in the National Kidney Foundation (National Kidney Foundation 2002). The majority of the studies (5 out of 7) were rated as moderate- or high quality by Balk et al. which indicates that the previously included studies were unlikely to cause major bias or omit information that limits the assessment. The assessment of study biases in the newly included studies by Ali et al. (2011) and Iqbal et al. (2009) was conducted using the Cochrane risk of bias tool. No serious risks of biases were identified in either of the additional studies (Table 10).

No serious indirectness of evidence was identified in the included studies of glucose intolerance populations. The additional studies by Ali et al. (Ali et al. 2011) and Iqbal et al. (Iqbal et al. 2009) recruited participants with impaired glucose tolerance, impaired fasting glucose or metabolic syndrome which are consistent with those included by Balk et al. (Balk et al. 2007).

In the impaired glucose tolerance population, the inclusion of Ali et al. (Ali et al. 2011) at two doses (500 and 1000 µg) and Iqbal et al.'s results had no significant bearing on the overall estimated mean and confidence interval of the effect of chromium on fasting blood glucose. The narrow confidence interval excludes any clinically significant changes in fasting blood glucose as a result of chromium supplementation. Therefore, this increases the certainty that chromium does not have an effect on fasting blood glucose levels in the impaired glucose tolerance population.

In the impaired glucose tolerance population, no serious inconsistency of results was observed as shown by low statistical heterogeneity ($I^2 = 0\%$, $P = 0.558$).

In the impaired glucose tolerance population, a range of different forms (mostly chromium chloride, but also included yeast, nicotinate, picolinate) and doses (ranged from 100 to 600 µg of elemental chromium) of chromium supplements were used. Ali et al. (Ali et al. 2011) used chromium picolinate at 500 and 1000 µg/d doses. It was unclear from the paper whether the doses quoted were elemental (500 or 1000 µg chromium/d) or complexed (62 or 124 µg chromium/d). Iqbal et al.'s RCT provided chromium treatment at 1000 µg chromium picolinate (124 µg elemental chromium/d), which is consistent with the previously included studies in Balk et al.'s review.

No serious concerns were found in the biases of included studies, indirectness of the included evidence, imprecision and inconsistency of the effect (as assessed by meta-analysis) and other methodological issues. Therefore, the review authors deemed that there is a moderate degree of certainty that chromium has no effect on blood glucose levels in the impaired glucose tolerance population.

8.2 Assessment of body of evidence

8.2.1 Consistency and causality of relationship

There is low degree of statistical heterogeneity ($I^2 = 0 - 0.4\%$) in the effect of chromium on blood glucose levels in the normoglycaemic and impaired glucose tolerance populations. Therefore, we rated the consistency for the lack of relationship to be 'Moderate.'

The causal relationship between chromium and blood glucose concentrations has not been established. RCT were included as a strong design for determining causality of relationship. Given the meta-analyses in both normoglycaemic and impaired glucose tolerance populations produced no effect of chromium on blood glucose levels, the degree of certainty for there being no causal relationship is 'Moderate.'

8.2.2 Plausibility

As discussed in 5.2.2.

8.3 Applicability to Australia and New Zealand

8.3.1 Intake required for effect

As there is no effect of chromium, no intake can be described. There was no effect of chromium intake on blood glucose levels across 5 – 924 µg chromium doses for a minimum of 3 weeks.

8.3.2 Target population

No specific population was identified prior to the review. The non-effect of chromium on blood glucose levels is relevant for normoglycaemic and impaired glucose tolerance adult populations. One study in overweight children suggests that the non-effect of chromium treatment may be applicable for children also.

For the purpose of this review, FSANZ has recommended to deem patients with DM to be out of scope for the assessment of this food-health relationship.

8.3.3 Extrapolation from supplements

As there is no effect of chromium, extrapolation from supplements is not required. If there was an effect, extrapolation of effect from supplemental doses to chromium intake from food sources would require caution.

9 Free-Living population – Conclusion

Based on the current body of evidence, including evaluation of factors and low risk of study biases, we conclude that there is a “Moderate” degree of certainty that there is no relationship between chromium intake and fasting blood glucose concentrations in normoglycaemic and glucose intolerance adult populations. One study in overweight children also found no effect of chromium supplementation on fasting blood glucose levels.

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Appendices

Appendix 1. Search items for systematic literature review

Deficiency population

PubMed

Search performed 28/5/15, 603 results

("chromium"[MeSH Terms] OR "chromium"[All Fields]) AND (("glucose"[MeSH Terms] OR "glucose"[All Fields]) OR ("blood glucose"[MeSH Terms] OR ("blood"[All Fields] AND "glucose"[All Fields]) OR "blood glucose"[All Fields] OR ("blood"[All Fields] AND "sugar"[All Fields]) OR "blood sugar"[All Fields]) OR ("insulin"[MeSH Terms] OR "insulin"[All Fields]) OR ("haemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated haemoglobin a"[All Fields] OR ("glycated"[All Fields] AND "haemoglobin"[All Fields]) OR "glycated haemoglobin"[All Fields]) OR ("haemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated haemoglobin a"[All Fields] OR "hba1c"[All Fields]) OR (glycaemic[All Fields] AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields]))) AND ("humans"[MeSH Terms] AND English[lang])

EMBASE

Search performed 28/5/15, 1105 results:

ID	Search	Results
1	exp chromium chloride/ or exp chromium phosphate/ or exp chromium blood level/ or exp chromium/ or chromium.mp. or exp chromium picolinate/	54636
2	glucose.mp. or exp glucose/ or exp glucose blood level/	663876
3	insulin.mp. or exp insulin blood level/ or exp insulin sensitivity/ or exp insulin/	594292
4	glycated hemoglobin.mp. or exp glycosylated haemoglobin/	18780
5	HbA1c.mp. or exp hemoglobin A1c/	59949
6	blood sugar.mp. or exp glucose blood level/	196427
7	exp glycemic control/ or glycaemic control.mp.	33360
8	2 or 3 or 4 or 5 or 6 or 7	1023588
9	1 and 8	2509
10	limit 9 to (human and English language)	1105

Cochrane Library

Search performed 28/5/15, 131 results:

There is 1 result from 8905 records for your search on 'chromium in Title, Abstract, Keywords and glucose OR blood sugar OR insulin OR glycated haemoglobin OR HbA1c OR glycaemic control in Title, Abstract, Keywords in Cochrane Reviews'

There are 5 results from 36795 records for your search on 'chromium in Title, Abstract, Keywords and glucose OR blood sugar OR insulin OR glyated haemoglobin OR HbA1c OR glycaemic control in Title, Abstract, Keywords in Other Reviews'

There are 125 results from 859632 records for your search on 'chromium in Title, Abstract, Keywords and glucose OR blood sugar OR insulin OR glyated haemoglobin OR HbA1c OR glycaemic control in Title, Abstract, Keywords in Trials

Free-living population

Commonwealth Agricultural Bureau

Search performed 17/7/15, 196 results:

You searched for: TS=(chromium) AND TS=(diabetes mellitus OR glycaemia OR glycosylated hemoglobin OR metabolic syndrome OR insulin resistance)

Timespan: 2006-2015. **Indexes:** CAB Abstracts.

MEDLINE

Search performed 17/7/15, 58 results:

# ▲	Searches	Results
1	Chromium/	11057
2	Diabetes Mellitus/	95185
3	Blood Glucose/ or glycaemia.mp.	136900
4	Hemoglobin A, Glycosylated/	24844
5	Metabolic Syndrome X/ or metabolic syndrome.mp.	32341
6	Insulin Resistance/	42607
7	2 or 3 or 4 or 5 or 6	276216
8	1 and 7	393
9	limit 8 to (english language and humans and yr="2006 -Current")	58

Appendix 2. Details on the 9 excluded studies that recruited participants we deemed unlikely to be 'chromium deficient'

Reference, study design	Objectives	Participants	Interventions ¹	Methods	Potential Confounders	Results	Notes
Anderson et al. (1988); RCT	To determine 1.) the intake and urinary excretion of Cr by trauma patients and 2.) if Cr supplementation above that normally present would be beneficial	Patients with various trauma Control group ($n = 8$): 27.4 ± 6.2 y, 13% females Cr supplementation group ($n = 7$): 34.7 ± 5.8 y, 43% females	IV CrCl_3 with TPN ($12 \mu\text{g/d}$, 1 week)	Patients randomised into Cr supplementation or control group for 1 week	Some patients received enteral nutrition with $\sim 20 \mu\text{g}$ Cr per 1000 calories	<ul style="list-style-type: none"> No improvement in serum glucose concentration with Cr Higher urinary Cr excretion in supplemented group 	<ul style="list-style-type: none"> 1 patient in supplement group died thereafter Participants unlikely to be chromium deficient
Carter et al. (1968); intervention trial	Investigated the possibility of Cr deficiency occurring in patients with kwashiorkor in Cairo, United Arab Republic	Infants diagnosed with Kwashiorkor malnutrition (age 0.5-3 y, males and females). 4 groups: Cr only ($n = 4$), nutritious hospital diet ($n = 9$), milk + Cr ($n = 5$), milk only ($n = 4$)	Oral CrCl_3 (single dose, $250 \mu\text{g}$ for Cr supplement only group; 3 days x $250 \mu\text{g}$ for milk + Cr group)	IVGTT completed on hospital admission; 4 different treatments provided (Cr only, hospital diet, milk + Cr or milk only); repeat IVGTT	Milk diet (3.5 g protein and 100 kcal/kg body weight)	<ul style="list-style-type: none"> No significant change in fasting glucose Glucose at 1h after infusion in IVGTT: 2/3 in Cr supplement group reported decreases, 2/3 in milk + Cr supplement group reported decreases 	<ul style="list-style-type: none"> Results presented as individual cases (only 6 cases with relevant data) Improvement in glycaemic control also seen in milk diet or hospital diet without added Cr
Drake et al. (2012); retrospective case series		Patients in intensive care unit ($n = 14$); transplants, cardiac procedures, oesophageal perforation, thymectomy (5/14 diabetes)	IV CrCl_3 infusion ($20 \mu\text{g/hr}$ for 12 hr; total 200-250 μg)	Retrospective review of hospital pharmacy records		<ul style="list-style-type: none"> Cr improved blood glucose levels and exogenous insulin requirement at 12 and 24 hr after initiation of infusion 	<ul style="list-style-type: none"> Retrospective study of hospital records 3/14 patients died subsequently
Gurson and Saner, (1971),	Investigating the effect of Cr on the	Infants with marasmic protein-energy	Oral CrCl_3 (single dose, $250 \mu\text{g}$)	IVGTT at hospital admission, oral Cr	All patients treated for	<ul style="list-style-type: none"> Cr treatment improved 	<ul style="list-style-type: none"> Two papers reporting data

Gurson and Saner (1973); case series	fasting blood sugar levels and glucose removal rates in cases of protein-calorie malnutrition of the marasmic Type	malnutrition ($n = 14$, mean age: 15 months, males and females)	given 1 day after hospital admission	treatment given, repeat IVGTT following day	malnutrition; protocol not specified	glucose removal rate in IVGTT in 9/14 cases	on the same study patients <ul style="list-style-type: none"> Individual data presented as responders and non-responders
Hopkins et al. (1968); case series	The effect of chromium(III) administration was investigated in malnourished Jordanian and Nigerian infants with hypoglycaemia and impaired glucose tolerance	Infants ($n = 12$, age range: 6 months – 2 y), diagnosed with malnutrition	Oral CrCl_3 (single dose, 250 μg) given 1-11 days after hospital admission	IVGTT 1-11 d after hospital admission, oral Cr treatment given, repeat IVGTT following day	All patients given treatment of reconstituted milk for malnutrition	<ul style="list-style-type: none"> Cr treatment improved glucose tolerance (glucose removal rate in IVGTT) in all 12 cases 	<ul style="list-style-type: none"> 6/12 cases were from Jordan, and 6/12 cases were from Nigeria Authors identified potential environmental and genetic susceptibility in response to Cr
Phung et al. (2010); case reports	The effect of IV Cr administration on glucose control in two patients receiving enteral nutrition is described	52 yo male with acute pancreatitis and Type 2 diabetes 53 yo male with trauma sustained by motor vehicle accident	IV CrCl_3 infusion (600 μg Cr in total over 4 days); initiated 12 days since hospital admission 3 infusions of IV CrCl_3 (435, 460, 684 μg Cr in total over 3 d days, respectively)	 1 st infusion 3 days after hospital admission, 2 nd infusion 3 days since end of 1 st and 3 rd infusion started 1 week after the end of 2 nd infusion	Enteral feeding with Pulmocare Enteral feeding with Resource 2.0	<ul style="list-style-type: none"> Improved average blood glucose range and exogenous insulin requirement Cr treatment led to lower requirement for exogenous insulin in all 3 infusions; slight improvement in average blood glucose after 2nd infusion 	<ul style="list-style-type: none"> Patient is unlikely to be Cr deficient
Surani et al. (2012); case report		62 yo female with septic shock, cardiac arrest, DM, coronary artery disease	IV CrCl_3 (3 $\mu\text{g}/\text{h}$ for 5 h), initiated 31 hours after hospital admission			<ul style="list-style-type: none"> Cr treatment decreased blood glucose levels and reduced 	

						exogenous insulin requirement	
Via et al. (2008); case report		76 yo female with aortic arch aneurysm and Type 2 DM	IV CrCl ₃ infusion (3 µg/h for 12 hours, total 60 µg); initiated 40 hours post operation			<ul style="list-style-type: none"> • Cr treatment reduced exogenous insulin requirement from 2110 U over 40 hours to nil 	Patient died shortly after
Wongseelashote et al. (2004); case series		Acute care patients requiring TPN (<i>n</i> = 5, age range: 20-79), range of medical issues	IV CrCl ₃ infusion (40 µg/d for 2 d); initiated 3-10 d from start of TPN	2 observation days, 2 days of Cr supplementation followed by 3 days of observation	TPN and requiring > 20 U/d exogenous insulin	<ul style="list-style-type: none"> • Cr treatment improved average blood glucose and reduced insulin requirement in 2/5 patients 	Favourable effects of Cr treatment persisted for 2 more days post-treatment

Appendix 3. Details of studies excluded at full-text screening for the free-living population

Study, reference	Exclusion reason
Albarracin and Fuqua (2007)	Cr supplementation with other treatment
Albarracin et al. 2008)	Cr supplementation with other treatment
Anderson (2008)	Review
Biswas et al. (2010)	Cr supplementation with other treatment
Dashkevich et al. (2013)	Not in English language
Diaz et al. (2008)	Cr supplementation with other treatment
Geohas et al. (2007)	Cr supplementation with other treatment
Griffiths (2014))	Review
Hamad et al. (2009)	Not a RCT
Kaats et al. (2011)	Cr supplementation with other treatment
Kalbasi et al. (2014)	Not in English language
Khosravi-Boroujeni et al. (2012)	Not a RCT
Kleefstra et al. (2006)	Already included in Balk et al.'s review
Krikorian et al. (2010)	Did not report glucose
Lapik et al. (2014)	Not in English language
Martin et al. (2006)	Already included in Balk et al.'s review
Pei et al. (2006)	Already included in Balk et al.'s review
Pohl et al. (2009)	Cr supplementation with other treatment
Racek et al. (2006)	Already included in Balk et al.'s review
Racek et al. (2013)	Not a RCT
Sandhu and Sachdeva (2013)	Did not report glucose

Appendix 4. GRADE summary of findings table

GRADE summary of findings table of updated systematic review (adapted from Balk et al. 2007 (Balk et al. 2007))

Question: What is the effect of increased chromium intake on blood glucose levels in normoglycaemic and impaired glucose tolerance populations?

Source: Critical appraisal and update of Balk et al.'s review (Balk et al. 2007), including three additional studies identified (Ali et al. 2011; Iqbal et al. 2009; Kim et al. 2011)

Quality Assessment of body of evidence							Participants ¹		Effect	Quality
Number of studies, strata	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Considerations	Parallel studies	Cross-over studies	Mean difference mmol/L (95% CI)	(degree of certainty in relationship)
Fasting blood glucose in normoglycaemic participants										
20, 23	RCT	Low ²	No serious inconsistency	Low	Low	Small sample size, limited reports of power calculations, potential confounding factors in study populations ³	322	0	-0.04 (-0.13, 0.05)	Moderate (<i>no effect</i>)
Fasting blood glucose in population with glucose intolerance										
9, 12	RCT	Low ⁴	No serious inconsistency	Low	Low	Small sample size, limited reports of power calculations, potential confounding factors in study populations	205	56	0.01 (-0.1, 0.13)	Moderate (<i>no effect</i>)

¹ Numbers of participants were extracted as per Figure 2, Balk et al.'s review in addition to the numbers of participants in the newly included studies (Ali et al. 2011; Iqbal et al. 2009; Kim et al. 2011).

² 12/19 studies from Balk et al.'s review classified as moderate quality which have some deficiencies in study designs but none likely to cause major bias, as assessed by Balk et al. (Balk et al. 2007), defined by the criteria described by National Kidney Foundation (National Kidney Foundation, 2002). The newly included study by Kim et al. (Kim et al. 2011) was determined to be not at serious risk of bias. Therefore, the totality of evidence is rated as being of low risk of bias.

³ Additional study (Kim et al. 2011) identified since Balk et al.'s review (Balk et al. 2007) was conducted in overweight children with normoglycaemic profile.

⁴ The majority of studies (5 out of 7) were rated as moderate or high quality by Balk et al. (Balk et al. 2007), which indicate that the studies were unlikely to cause major bias, using the criteria described by the National Kidney Foundation (National Kidney Foundation, 2002). The two newly included studies (Ali et al. 2011; Iqbal et al. 2009) were determined to be not at serious risk of biases. Therefore, the totality of evidence is rated as being of low risk of bias.