

Protocol: The relationship between vitamin A and body mass: A systematic review and meta-analysis

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Abstract

The proposed protocol is for a systematic review and meta-analysis on the relationship between vitamin A and body mass. The primary objective is to explore the mechanisms between vitamin A and adiposity such as inflammation, dietary intake and body fat. The secondary objective is to look at the extent to which vitamin A is stored in different adipose tissue depots. The protocol outlines the motive and scope for the review, and methodology including the risk of bias, statistical analysis, screening and study criteria.

1 Background

1.1 The problem, condition or issue

Globally, an estimated 1.9 billion people are either overweight or obese (WHO et al, 2017). It is well known that obesity is a leading cause for many non-communicable chronic diseases (NCDs) including cardiovascular disease, hypertension, type 2 diabetes (T2D) and cancer. More recently, micronutrient deficiency has been found in obese individuals in Vietnam and Latin American countries such as Mexico and Brazil (Laillou et al, 2014; Garcia et al, 2013; de Souza et al, 2007). Together, these two burdens constitute the double burden of malnutrition. There is increasing evidence indicating an inverse association between micronutrients and individuals with a higher body mass index (BMI), in particular fat soluble vitamins such as vitamin A (Andersen et al, 2006; Suzuki et al, 2006). These studies have also shown that dietary intakes of normal weight, overweight and obese individuals are not drastically different. Moreover, animal studies confirmed that obesity causes vitamin A deficiency, as vitamin A levels and transcriptional signalling is reduced in multiple organs, when serum vitamin A concentrations are in the normal range (Trasino et al, 2015).

In humans, low serum vitamin A concentrations have been observed in obese individuals, most likely due to increased uptake into the adipose tissue depot, which is acting as a major body pool for vitamin A (Osth et al, 2014; Bonet et al, 2012; Bonet et al, 2003). Although, there is considerable evidence showing similar observations for other vitamins such as vitamin D, vitamin A plays a key role in the regulation of genes involved in fatty acid oxidation and lipid metabolism (Saneei et al, 2013). Vitamin A has been shown to be associated with a reduced odds of metabolic syndrome (MS), non alcoholic fatty acid liver disease (NAFLD) and dyslipidemia (Beydoun et al, 2012; Botella-Carretero et al, 2010; Albuquerque et al, 2016). Therefore, adequate vitamin A status in key metabolic tissues may lead to favourable reductions in body fat and subsequently reductions in obesity.

However, it is not clear if an increase in adiposity is a causal effect of low serum vitamin A concentrations or the result of other physiological and environmental factors (Garcia et al, 2009). For instance, inflammation and dietary intake have been implicated as reasons for reduced serum vitamin A concentrations (Hosseini et al, 2017). Therefore, the proposed review hopes to show the degree at which inflammation and dietary intake each effect serum vitamin A concentrations of obese individuals. The review hopes to not only elucidate these effects but show the extent at which different adipose tissue depots reflect vitamin A storage.

1.2 The intervention

The aetiology of obesity is complex and is not confined to a single cause or population. However, at a population level, rapid urbanisation and economic shift in developing countries has shifted from traditional diets which are often high in

fruit and vegetables towards a westernised diet; High in trans fats and refined sugars (Zeba et al, 2014; Shrimpton and Rokx, 2012). High fat foods have become readily available and cheap to buy, therefore, the DBM is associated with high socioeconomic status in developing countries and low socioeconomic status in developed countries (Zeba et al, 2014; Min et al, 2018; Shrimpton and Rokx et al, 2012). Regions affected include Latin America, Africa, the middle East and Asia (Laillou et al, 2014; et al, 2009; Gera et al, 2000; Kim et al, 2011). Children and adolescents are probably the most important individuals in societies as childhood obesity strongly predicts the likelihood of NCDs later in life (Shrimpton and Rokx, 2012).

Vitamin A is of particular interest because of its role in body fat regulation and abundance in fruit and vegetables (Gibney et al, 2002). A number of cross-sectional studies have shown that high vitamin A intakes are associated with a reduced odds of metabolic syndrome (Beydoun et al, 2012; Beydoun et al, 2011). Most of these studies also show that serum vitamin A concentrations are inversely associated with body mass. Women have been shown to have lower vitamin A serum concentrations than men (Suzuki et al, 2006; Palli et al, 1999). This is also reflected at the population level where higher rates of obesity are found in women rather than men (Shrimpton and Rokx, 2012). Similar findings have been shown for obese children and adolescents (de Souza et al, 2007; Garcia et al, 2013).

1.3 What are the potential mechanisms behind the low plasma vitamin A observed in overweight and obese subjects?

The DBM is believed to be caused by a wide range of factors such as a shift in nutrition, demographics and epidemiology (Shrimpton and Rokx et al, 2012). These factors are well documented but the potential mechanisms at the individual level are still not fully understood.

It has only been shown in the last decade that organs other than the liver and small intestines have the capacity to metabolise and store molecules (Coelho et al, 2013). Adipose tissue has been coined as a major endocrine organ and amongst its many secretory products is retinol binding protein (RBP) (Frey et al, 2011). RBP involves the binding of retinol (preformed vitamin A) and is secreted in order to maintain serum retinol concentrations (Gottesman et al, 2001). Elevated RBP has been shown to correlate with adiposity (Aeberli et al, 2007; Castro et al, 2014). Low serum retinol concentrations have been observed in obese subjects which may be because RBP is excreted in response to low adipose retinol concentrations, leading to a higher RBP to retinol ratio (Botella-Carretero et al, 2010; Mills et al, 2009). The appearance of low serum carotenoids (provitamin A) has also been observed in obese subjects. However, unlike retinol, provitamin A (carotenoids) is not bound to RBP, therefore, the mechanisms of uptake are different. The appearance of low serum carotenoids has been suggested to be due to adipose tissue acting like a passive sink (Albuquerque et al, 2016; Osth et al, 2014).

The absorption of vitamin A may be reduced in overweight and obese subjects. A low conversion rate of very low density lipoprotein (VLDL) to low density lipoprotein (LDL) has been reported in obese individuals (Egusa et al, 1985; Chan et

al, 2004). LDL is secreted from the liver and is responsible for delivering vitamin A (retinyl esters and carotenoids) to organs in the body (Gibney et al, 2002).

The low conversion rate may also be influenced by various amounts of vitamin A intake. High doses of vitamin A have been associated with hypertriglyceridemia; A known side effect of retinoid therapy (Miller et al, 1997). Human cell studies have suggested a role of peroxisome proliferator activator receptors (PPARs) (Morikawa et al, 2013; Ribalta et al, 1997). PPARs are a set of steroid hormone receptors which are key regulators of fat metabolism. PPARs are able to form heterodimers with retinoid X receptors, in particular PPAR γ . The activation of PPAR γ by retinoic acid (a preformed vitamin A metabolite) leads to the downregulation of its target gene lipoprotein lipase (LPL) (Bonet et al, 2012). LPL role is well documented for breaking down triacylglycerols (TAG) in LDL and chylomicrons (Lanham-New et al, 2011). Subsequently, the inhibition of LPL would lead to high VLDL, high serum TAG and low LDL.

An increase in adiposity is also known to cause systemic inflammation through excretion of inflammatory markers such as c-reactive protein, leptin, interleukins and tumour necrosis factors (Rubin et al, 2017). Key metabolic enzymes responsible for vitamin A uptake such as RBP-4 have been shown to be inhibited by these markers which would lead to reduced vitamin A uptake of multiple organs.

1.4 Why it is important to do the review

With a large body evidence suggesting an association of vitamin A with body mass and its reduced odds of metabolic syndrome. Vitamin A intake may have important implications for childhood obesity, NCDs and the obesity epidemic worldwide (Noy et al, 2013).

Beydoun et al (2018) published a systematic review and meta-analysis looking at the serum concentrations of vitamin A in individuals with metabolic syndrome but did not include individuals with other NCDs as a consequence of obesity. Therefore, individuals with dyslipidemia, NAFLD and T2D were left out. The review had adopted a score based study quality assessment. The problems of score based study quality assessment are well known (Higgins et al, 2011). It is envisaged that bias will be particularly high in these studies because they are observational and confounding of effect is likely. Another systematic review had looked at the relationship of antioxidants with body mass index (Hosseini et al, 2017). However, they have not shown this meta-analytically. To our knowledge, there is no systematic review and meta-analysis looking at multiple mechanisms of vitamin A and body mass and followed the guidelines for the formation of a high quality systematic review; Based on campbells Methodological Expectations of Campbell Collaboration Intervention Reviews (MECCIR).

The proposed review will adopt not just a univariate meta-analysis but also a multivariate meta-analysis (Riley et al, 2017). Multivariate meta-analyses have rarely been used in nutritional research. A multivariate meta-analysis has the potential to form more robust evidence to help inform policy and reduce bias by combining multiple effect sizes.

2 Objectives

Our primary research question is:

1. What is the major contributing factor for low serum vitamin A (i.e. retinoids and carotenoids) observed in overweight and obese individuals?

Our secondary research question is:

1. To what extent is vitamin A stored in adipose tissue?
2. To what extent do vitamin A stores differ in different adipose tissue depots?

3 Methodology

3.1 Criteria for including and excluding studies

Types of study designs

Observational studies including cohorts, cross-sectional studies and case-control studies looking at serum retinol, serum carotenoids, vitamin A intake and vitamin A concentrations of different adipose tissue depots will be considered. Randomised controlled trials (RCTs) looking at the effects of vitamin A intake on body weight will also be considered.

Types of participants

Participants of either sex, all ages and demographics will be considered in observational studies and RCTs. These will include cases of diseases associated with obesity (non-alcoholic fatty liver disease, type 2 diabetes, dyslipidemia or metabolic syndrome) or individuals with a body mass index (BMI) of 25 kg/m² or more (WHO, 2000). Studies must include some form of control group without the disease and with a body mass index less than <25kg/m² (WHO, 2000).

Types of interventions

Observational studies that look at obese or overweight individuals as defined based on the World Health Organisation's criteria will be considered (WHO, 2000). Studies looking at vitamin A concentrations in different adipose tissue depots of all types of individuals (i.e. normal weight, obese or overweight) will be considered. RCTs that provide obese, overweight or normal weight individuals with vitamin A supplements or vitamin A rich foods will be considered.

Types of outcome measures

Observational studies that report serum carotenoids, serum retinoids, body mass index, dietary intake and vitamin A concentrations of different adipose tissue depots will be considered as primary outcomes. If observational studies report other markers of obesity such as cholesterol (LDL and HDL), fasting glucose and TAG these will be considered as secondary outcomes. RCTs that report body weight after the intervention will be considered as primary outcomes.

Duration of follow-up

All follow-up lengths or study durations will be considered.

Search strategy

A sample of journal articles will be sourced from a single database (Medline, pubMed, Web of Science or Cochrane central register of controlled trials) and common phrases will be picked from titles to form initial search terms (Table 1). These search terms will then be used with boolean operators in four databases; Medline, pubMed, Web of Science and

Cochrane central register of controlled trials. Database thesauruses will be used to optimise search terms for each database.

Table 1. Example of search terms that will be used to identify observational studies

Field	Search term(s)
All	("Vitamin A" OR retinol OR retinoic acid OR retinyl esters OR retinol binding protein OR polar retinoid metabolites OR carotene OR carotenoids OR retinoids OR preformed vitamin A OR serum carotenoids OR lutein OR zeaxanthin OR lycopene)
AND	
All	(children OR adults OR adolescents)
AND	
All	(metabolic syndrome OR non alcoholic fatty liver disease OR obese OR overweight OR body mass index)
AND	
All	(cohort OR observational OR prospective OR dietary intake OR dietary factors OR food groups OR double burden OR nutrient status OR micronutrient status)

Searches will not be restricted by years, title or language. Key authors will be contacted for latest publications and their existing publications will be searched for relevant articles. Studies included in the latest literature reviews will also be retrieved.

Critical appraisal

Cochranes risk of bias tool will be used to assess all observational studies and randomized controlled trials. Observational studies will use ROBINS risk of bias tool as unlike other risk of bias tools, ROBINS takes into account internal validity and attempts to mimic a randomised control trial (Sterne et al, 2016). This allows for more rigorous evaluation of bias that can arise from potential confounding of the effect, recall bias, differential misclassification of outcome and/or intervention status, attrition bias, reporting bias and detection bias. These forms of bias may inform reasons for heterogeneity in effect sizes. However, it is important to understand that not all outcomes in a study will be affected by the same bias. For instance, reporting bias may be detected in interviews or food frequency questionnaires but this may not be applicable for data from analysis of blood samples. Therefore, risk of bias must be carefully judged across all outcomes included in

studies. For RCT studies, Cochran's risk of bias tool for RCTs will be adopted (Higgins et al, 2011). RCTs will be screened for selection, detection, attrition and reporting bias.

Risk of bias will be accompanied by funnel plots to assess publication bias (Higgins et al, 2011). Based on each study's overall bias, sensitivity analyses will be conducted to assess robustness of results in the presence of studies that are at high risk of bias. No study will be excluded based on the critical appraisal assessment but this information will be graded for the quality of evidence using Cochran's GRADE criteria (Schünemann et al, 2013).

Description of methods used in primary research

Observational studies such as cohorts, cross-sectional and case-control studies involve random sampling from a population that meet a specific eligibility criteria. Currently, there are very few cohort studies that look at the relationship of vitamin A with body mass over time. For instance, the CARDIA study is the only published cohort that assesses the association of serum carotenoids with body mass index (Andersen et al, 2006). The reasons for this may be because cohorts involve assessing a large number of participants which are very costly. Therefore, the majority of cohorts employ non-repeatable laboratory measurements such as food frequency questionnaires. Nonetheless, cohorts provide valuable information on dietary intake patterns of vitamins, in particular vitamin A (Sun et al, 2014; Galan et al, 2005).

Cross-sectional studies like cohorts are observational. They differ from cohorts in that the participants are not followed over a long period of time and information is collected only once. The majority of cross-sectional studies involve laboratory measurements, food frequency questionnaires and/or 24 hour recalls. Thus, there is a considerable amount of cross-sectional studies looking at both dietary intake of individuals and serum concentrations of nutrients (Li et al, 2013; Wang et al, 2008). The majority of cross-sectional studies are based on a subsample of individuals from a larger epidemiological study such as a cohort or a national health and examination survey (Wang et al, 2008; Cheng et al, 2017; Beydoun et al, 2012).

Case-control studies involve collecting data from a selection of healthy individuals that are not at risk of an exposure and individuals that are exposed. For instance, cases may be individuals with MS, T2D, NAFLD or overweight subjects and the controls without the disease or with a BMI of $<25\text{kg/m}^2$ (Godala et al, 2016; Van Campenhout et al, 2006; Botella-Carretero et al, 2010). Most case-control studies involve collecting data on dietary intake using 24 hour recalls, by interview, food diaries or FFQs. They may also involve the collection of blood samples and anthropometric data.

There are a few observational studies which have also looked at vitamin A concentrations in different adipose tissue depots (Osth et al, 2014; Chung et al, 2009). These studies involve invasive procedures such as the collection of adipocytes or tissue samples.

RCTs assessing weight loss after vitamin A intervention are scarce (Bonet et al, 2015; Teas et al, 2009). However, there are a handful of studies that have administered supplements and recorded body weight after dietary intervention.

Criteria for determination of independent findings

Most cohorts, case-control and cross-sectional studies that look at serum concentrations of nutrients in relation to diseases associated with obesity report findings by the components of the disease rather than quantiles, quartiles or tertiles. For instance, the Tehran lipid and glucose study reports nutrient intake for individuals with insulin resistance and individuals without (Mirmiran et al, 2016). Studies that report MS sometimes split participants by the number of MS components observed (Cheng et al, 2017). In these cases, individuals with insulin resistance or with the most components of MS will have a BMI of $>25\text{kg/m}^2$ and the controls will be individuals with no components of MS or with a BMI of $<25\text{kg/m}^2$. Studies that directly look at the relationship of body mass and nutrient concentrations normally have nutrients divided by category of body mass index or percentile (Andersen et al, 2006; Ford et al, 2002).

Observational studies that have looked at the vitamin A status of different adipose tissue depots report the concentration of carotenoids per gram of body fat or concentration (Osth et al, 2014; Chung et al, 2009).

The few RCTs that have looked at weight loss in individuals after vitamin A intake will most likely report body weight before and after the intervention (Teas et al, 2009).

Details of study coding categories

Studies should include:

- Individuals with a disease as a consequence of obesity (T2D, dyslipidemia, insulin resistance, MS and NAFLD) or overweight individuals. Controls should be apparently healthy and a normal weight.
- Serum carotenoids and retinol and vitamin A intake as primary outcomes and if available serum triglycerides, cholesterol or fasting glucose.
- Participants of any ethnicity, demographic and sex.
- Participants from any country.
- Studies in any languages.

Statistical procedures and conventions

For the first part of the review, data from observational studies will be compiled in an excel sheet and will be sorted based on participants age, participants sex, study location, disease type, body mass index and study type. All outcome measures outlined previously will be collected in a single sheet before being transferred to separate sheets where data will be converted into common units. Studies that report standard errors (SE), interquartile ranges (IQR) or confidence intervals (CI) will be converted to standard deviations (SD) (Figure 1) (Borenstein et al, 2009; Wan et al, 2014). A bootstrapping procedure will be conducted in R programming for studies that do not report IQR, SD, CI or SE.

$$SD = SE\sqrt{n} \quad \mathbf{A}$$

$$SD = \sqrt{n} \frac{(LB+UB/2)-LB}{1.96} \quad \mathbf{B}$$

$$SD = \frac{q^3 - q^1}{2\Phi\left(\frac{0.75n - 0.125}{n + 0.25}\right)} \quad \mathbf{C}$$

Figure 1: Formula to estimate SD when given the SE (**A**). Formula to estimate the SD when given confidence intervals (**B**) Formula to estimate SD when given IQR (**C**) (Borenstein et al, 2009; Wan et al, 2014)

The metafor package in R programming will be used to compute the standardised mean difference (SMD) for study outcomes such as carotenoids, retinoids, glucose, TAG and cholesterol (LDL and/or HDL). SMDs will be between overweight subjects and normal weight controls. SMDs have been chosen as this will converge all biomarkers on a common scale (z-score). This will prevent the likelihood of a negative definite matrix when calculating a variance-covariance matrix for the multivariate meta-analysis. The variance-covariance matrix will require additional calculations such as the correlation and covariance between effect sizes. A pearson correlation is required to calculate the covariance between the effect sizes. These are rarely reported in studies so this will be estimated from studies that contribute each outcome as described by Kirkham et al (2012) (Crawley et al, 2007) (Figure 2, A). Covariance will be calculated as described by Gleser and Olkins (2009) (Figure 2, B). A borrow of strength value which describes the additional strength obtained from a multivariate meta-analysis over a univariate meta-analysis will be estimated as described by Jackson et al (2017) (Figure 2, C). Model parameterization will be assessed based on log-likelihood plots.

$$p = \frac{\sigma_1 + \sigma_2 - \sigma_1 - \sigma_2}{\sqrt{2}\sigma_1\sigma_2} \quad \mathbf{A}$$

$$\text{Cov}(d_{jt}, d_{kt}) \approx r_{jk} \left(\frac{1}{n_0} + \frac{1}{n_t} \right) + \frac{r_{jk}^2 d_{jt} d_{kt}}{2(N - T - 1)} \quad \mathbf{B}$$

$$BoS_r^{RV} = 1 - \frac{\text{var}(\hat{\beta}_{mv,r})}{\text{var}(\hat{\beta}_{uv,r})} \quad \mathbf{C}$$

Figure 2: Formula to estimate correlation coefficient between two SMD (**A**). Formula to estimate covariance between two SMD (**B**) Formula to estimate the borrow of strength (**B**) (Crawley et al, 2007; Pustejovsky, 2015; Jackson et al, 2017)

Although, it is not known yet how many outcomes can contribute to the multivariate meta-analysis, it can be assumed that studies which report body mass data will also report glucose, cholesterol or TAG; Biomarkers associated with obesity.

Forest plots will be produced for serum carotenoids, serum retinoids and vitamin A dietary intake with both the univariate summary measure and multivariate summary. Forest plots will be subgrouped into children/adolescents and adults. Heterogeneity will be interpreted as I^2 . Funnel plots will be produced for each biomarker to assess publication bias.

Treatment of qualitative research

Information will be collected on participants body mass index or body mass, type of disease, age, sex, number of participants, duration of study and adjustments made to outcomes (Table 3).

Table 3: Example table for observational studies

Author(s) and Year	Topic	Location	Study type	Duration	*Sex	Age	Participants (n)	Intervention group BMI	Control group BMI	Population	Measurement(s)	Adjustments
Galan et al, 2005	Dietary status	USA	Cohort	7.54y	M/F	Adults	762	>30	<25	The SU.VI.MAX Study.	Serum carotenoids (beta-carotene)	-

a= M=Male, F=Female

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Roles and responsibilities

Content: Prof Georg Lietz and Dr Anthony Oxley have written a number of articles on primary research of carotenoids and are highly active in the area of inter-intra individual variation of vitamin A stores. Wasim Iqbal and Kieran Finney have worked on other research projects in relation to whole-grains and has shown a considerable interest in the area of nutrient kinetics.

Systematic review methods: Gavin Stewart has considerable experience in the formation of systematic reviews and meta-analyses.

Statistical analysis: Gavin Stewart has considerable experience in statistical methods and is an expert in bayesian statistics. Wasim Iqbal has conducted relevant statistical analysis and is competent in R programming.

Information retrieval: Wasim Iqbal, Kieran Finney and Ines Mendes are experienced in information retrieval and boolean searches.

Sources of support

There is no funding for this review.

Declarations of interest

Prof Georg Lietz is a member of the international carotenoid society, american nutrition society and european nutrition leadership programme alumni association.

Gavin Stewart is an editor for Peer J, research synthesis methods and Cochrane/Campbell collaborations.