Effects of starch on oral health: systematic review to inform WHO Guideline

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Abstract

A systematic review was conducted to update evidence on the effect of total dietary starch, and on the effect of replacing rapidly digestible starches (RDS) with slowly digestible starches (SDS) on oral health outcomes, to inform updating of World Health Organization Guidance on carbohydrate intake. Data sources included MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, LILACS and Wanfang. Eligible studies were comparative and reported any intervention with a different starch content of diet(s) or food(s) and data on oral health outcomes relating to either dental caries, periodontal disease or oral cancer. Both studies that reported total dietary starch intake or change in starch intake were included, or where comparisons/exposure included diet(s)/food(s) that compared RDS and/or SDS. The review was conducted in accordance with the PRISMA statement, and evidence was assessed using the GRADE Working Group Guidelines.

From 6080 papers identified, 33 papers (28 studies) were included in the RDS/SDS comparison: 15 papers (14 studies) assessed the relationship between SDS and/or RDS and dental caries, 16 papers (12 studies) considered oral cancer and 2 studies periodontal disease. For total starch, 23 papers (22 studies) were included: 22 assessed the effects on dental caries and one considered oral cancer.

GRADE assessment indicated ‘low’ quality evidence suggesting no association between total starch intake and caries risk, but that RDS intake may significantly increase caries risk. ‘Very low’ quality evidence suggested no association between total starch and oral cancer risk and ‘low’ quality evidence suggested SDS decreases oral cancer risk. Data on RDS and oral cancer risk was inconclusive. ‘Very low’ quality data relating to periodontitis suggested a protective effect of wholegrain starches (SDS). The best available evidence suggests only RDS adversely affect oral health.

Introduction

Current global dietary guidelines recommend a diet rich in carbohydrate (>55% energy) (FAO/WHO 1998) and low in free sugars (<5-10% energy) (WHO 2015), thus indicating a high proportion of energy should be provided by starch. Starch is heterogeneous in nature and starch types with different physiological properties may have different impacts on health (Cummings and Stephen 2007) including oral health. The classification of rapidly digestible starch (RDS), slowly digestible starch (SDS) and resistant starch (RS) (Englyst et al 1992) was recognised. RDS (e.g. processed starches) are digested rapidly, while SDS (e.g. wholegrains, legumes) are digested slowly in the small intestine and RS (e.g. un-gelatinised starch) non-digestible. Previous reviews of starch intake on oral health have presented inconclusive evidence. The British Scientific Advisory Committee on Nutrition (SACN 2012) concluded there was a lack of available evidence on the relationship between total starch intake and oral health. The World Cancer Research Fund (WCRF) 2007 consultation was unable to make firm conclusions regarding cereals (grains) and their products, starchy roots, tubers and plantains or other starchy foods and the risk of cancer of the mouth, pharynx and larynx.

With a view to updating global recommendations for carbohydrates including starch, the WHO commissioned a systematic review on starch and its effects on oral health as part of its guideline development process (WHO 2014). The objectives were to systematically review all available published evidence pertaining to the effect on oral health outcomes of replacing rapidly digestible starches (RDS) with slowly digestible starches (SDS) in the diet and the impact of total starch intake on oral health outcomes. The overall questions underpinning the review was ‘what is the effect of an increase in the intake of total starch and of replacing RDS with SDS on oral health (including periodontal disease, dental caries and oral cancer)?’ The specific questions are presented in Table 1.

Methods

Guided by the WHO Guideline Development Process (WHO 2014) a systematic review was conducted and reported according to the PRISMA statement (www.prisma-statement.org). The protocol is available as Supplementary Material 1 (Protocol).

Eligibility criteria

All relevant randomised controlled trials (RCTs), non-randomised intervention studies and observational studies (including cohort, case-control, population, ecological and cross-sectional studies), as well as non-epidemiological human experimental studies (e.g. enamel/dentine slab and plaque pH studies as proxies for caries risk) were included. Animal studies were excluded due to differences between animals and humans in tooth morphology, plaque bacterial ecology, salivary flow and form of dietary starch consumed.
Participants were humans in low, middle and high income countries. All age groups were included. No date or language restrictions were used. For RCTs an intervention a follow up period of at least one year for dental caries (adequate duration for an effect on dental caries increment to be observed) or at least three months for periodontal disease (a usual minimum follow up period for periodontal intervention studies) was required.

Studies were included if they reported any intervention with a different starch content of diet(s) or food(s) in one arm of the study and also included data on oral health outcomes relating to either dental caries (e.g. prevalence of dental caries, change in dental caries, or comparison of higher vs. lower caries), periodontal disease (e.g. indices of periodontitis, change in indices of periodontitis, or high vs. lower values) or oral cancer (presence or absence of oral cancer). Observational studies were included if they reported starch intake or change in starch intake or where comparisons/exposure included diet(s)/food(s) which compared RDS and/or SDS.

RDS included starches that are digested rapidly in the small intestine and SDS included starches that are slowly digested (Cummings and Stephen 2007). However, for the purpose of the Guideline Development Process, RDS vs. SDS comparisons also included: lower versus higher resistant starch intake; lower versus higher legume intakes; higher versus lower starch plus sugars; highly processed versus less processed starch foods; starch-influenced diet versus normal diet; refined carbohydrate compared with wholegrain carbohydrate; carbohydrates with higher compared with lower glycaemic response. Starch was expressed in mg or g/day, kg/year, or as percent energy from starch.

Dental caries outcomes included caries prevalence, incidence and/or severity measured as DMF Index, DMFT, dmft, DMFS, defs, deft, dft or comparisons between higher caries vs. lower caries and for laboratory studies, plaque pH and measures of demineralisation. Oral cancer included cancers of the mouth, pharynx (oropharynx) and throat (hypopharynx and larynx), and cancers of the oesophagus and nasopharynx where analysis was combined with cancers of the oropharynx meaning that cancer of the oropharynx could not be analysed separately. Studies reporting cancer of the upper gastrointestinal (GI) tract were included as clinical definitions of this includes many relevant cancers. Periodontal disease (adult periodontitis) outcomes included Basic Periodontal Examination, Bleeding, Periodontal, Gingival indices and periodontal pocket depth.

Search Strategy

Six electronic databases were searched in September 2016, with update searches undertaken in March 2017. The databases included MEDLINE and Embase, databases specific for trials (Cochrane Central Register of Controlled Trials) and systematic reviews (Cochrane Database of Systematic Reviews), LILACS (Latin American and Caribbean Health Sciences) and Wanfang (China). Hand searches of citation lists of identified reviews and expert consultation were conducted to identify further studies. Abstracts and unpublished studies were not included. The search strategy is presented in Supplementary Material 2 (Search Strategy).

Study selection

Retrieved records (titles and/or abstracts) were screened by one person to exclude studies clearly outside the scope of the review. The remaining records underwent independent duplicate screening (KH and JL). Disagreements between the reviewers was resolved by consensus with involvement of a third researcher (PM) where necessary. Evidence was grouped into the three oral diseases (caries, periodontal disease, oral cancer) and each organised by study type: cohort, case-control, cross-sectional, non-randomised intervention and experimental, to enable data synthesis of the 'best available evidence' (Petticrew and Roberts 2006). Best available evidence synthesis uses the best evidence in terms of study design but with a lower level of relevant evidence still being considered for inclusion.

Data extraction was undertaken by one reviewer and checked by a second reviewer. Information from the data extraction for each paper is presented in Supplementary Material 3 (Included Studies). Meta-analysis and forest plots of data that could be pooled, were created using STATA 14.1 software. Evidence was also reported narratively.

Quality Assessment

In line with the WHO Guideline Development Process (WHO 2014) the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) (Atkins et al. GRADE Working Group, 2004) was used to assess the quality of evidence in relation to each review question. The quality of the evidence was categorised as high, moderate, low or very low. GRADE Evidence Profiles are presented in the Appendix (Supplementary Material 4 (Grade Evidence Profiles)).

Results

The Fig. presents a Prisma flow chart. From all databases combined, 6080 papers were identified. After screening, 156 full text papers were assessed for inclusion (by two reviewers). For the RDS vs. SDS comparison, 33 papers (28 studies) were included of which 15 (14 studies) related to dental caries, 16 (12 studies) to oral cancer and 2 (2 studies) to periodontal disease. For total starch 23 papers (22 studies) met the inclusion criteria, 22 (21 studies) on dental caries and one on oral cancer. Excluded were 123 studies (for the RDS/SDS comparison) and 51 of the 74 papers assessed for total starch, summarised in Supplementary Material 5 (Characteristics of Excluded Studies).

Dental caries

The analysis for total starch included 8 epidemiological (4 cohort, (Campain et al. 2003; Kaye et al. 2015; Marshall et al. 2005; Rugg-Gunn et al. 1987); 2 cross-sectional (Arcella et al. 2002; Papas et al. 1995); 1 ecological (Fisher 1968; Holloway et al. 1963); 1 non-randomised intervention (Scheinin and Mäkinen 1975) (Table 2) and 13 experimental laboratory studies (6 enamel/dentine demineralisation studies, 4 plaque pH studies, 2 that measured both demineralisation and plaque pH, and one study measured salivary glucose/lactic acid) (detailed in Appendix Table 15). Data from epidemiological studies were not suitable for pooling. Cohort studies consistently showed no association between total starch and caries. Assessing these studies via GRADE classified the data as ‘low quality’. Data from two cross-sectional studies (Arcella et al. 2002; Papas et al. 1995) suggested starch increased risk of dental caries when combined with sugars. Though demineralisation studies showed starch (RDS) could cause demineralisaton after 45 minutes exposure (Brudevold et al. 1988; Kashket et al. 1994), exposure <45 minutes and raw starch did not (Brudevold et al. 1985), and plaque pH studies generally showed starch did not decrease plaque pH to <5.5 (critical pH) in the absence of sugars (Supplementary Material 6 - Experimental Studies).

The analysis of RDS vs. SDS included 4 epidemiological (2 cohort (Campain et al. 2003; Chankanka et al. 2011), 1 cross sectional (Llena and Forner 2008), 1 ecological (Sreebny 1983)) (Table 2) and 10 experimental studies (6 enamel slab, 4 plaque pH) (Supplementary material Table 15). Data from these studies were not suitable for pooling due to heterogeneity in design, outcomes, dietary exposure and demographic characteristics. The cohort studies were the best available evidence for assessing via GRADE methodology; both studies were conducted in children and accounted for fluoride exposure. Both showed a positive association between RDS and the caries risk. The quality of evidence for an increase in caries with an increase in intake of RDS was categorised as 'low' (Supplementary material 4 - Grade Evidence Profiles). Data from experimental studies were consistent with these findings (Supplementary Material 6: Details of Experimental Studies).

Oral cancer

No association was found between total starch intake and oral cancer based on the one included study (OR (95% CI) =0.77 (0.51, 1.17) (Bravi et al. 2013).

Of the 12 included studies, 7 (2 cohort (Kasum et al. 2002; Lam et al. 2011); 5 case control (Aune et al. 2009; Bosetti et al. 2000; Giraldi et al. 2016; McLaughlin et al. 1988; Chen et al. 2016) provided data pertaining to SDS and risk of oral cancer and 5 (4 case-control (Bravi et al. 2013; Chatenoud et al. 1999; Franceschi et al. 1999; Levi et al. 2000) and one ecological (Hebert et al. (1993)) to RDS and oral cancer (Table 3).

With respect to SDS, meta-analysis of data from two cohort studies relating to impact of wholegrain starch-containing foods showed a significant reduction (38%) in risk of oral cancer for females (Hazard Ratio (95% CI) 0.62 (0.45, 0.80) (see Appendix for Forest plot). Assessment via GRADE ranked this evidence as 'low quality' (Supplementary Material 4). Data from two case-control studies were consistent with this finding (Bosetti et al. 2000; Levi et al. 2000). Data from case-control studies on legume intake (SDS) and oral cancer showed null or negative effects (Aune et al. 2009; Giraldi et al. 2016; McLaughlin et al. 1988; 陈法 et al. 2016). Assessment of these data via GRADE classified the evidence as 'low' quality (Supplementary material 4).

With respect to RDS, meta-analysis of data from two case-control studies of refined grain intake (Chatenoud et al. 1999; Levi et al. 2000) showed low quality evidence of an increased risk of oral cancer with increased RDS (OR (95% CI) = 1.64 (1.17, 2.10) (see Appendix). Meta-analysis of data from two case-control studies of RDS in the form of potatoes were inconclusive (OR (95% CI) =1.41 (0.68, 2.13).

Periodontal Disease

One cohort study providing a comparison of RDS vs. SDS and risk of periodontitis (Merchant et al. 2006) showed those consuming 3.4 servings (median) of wholegrain foods compared with <0.3 servings had a significantly (23%) reduced risk of periodontitis (multivariate relative risk (95% CI) = 0.77 (0.66, 0.89) (see Appendix). Risk of periodontitis was not significantly related to intake of refined grains (RDS) (multivariate relative risk (95% CI) 1.04 (0.89, 1.23). The one cross-sectional study of a representative sample of 6,052 adults in the US (Nielsen et al. 2016) found that low intake of wholegrain was associated with increased risk of periodontitis (fully adjusted OR (95% CI) = 1.32 (1.08,1.62) (Appendix Table 3)). Grade Evidence Profiles rated the evidence on periodontal diseases as very low quality.

Discussion

Based on the evidence available, only rapidly digestible starch (e.g. more processed starches) increases risk of dental caries. There is very limited evidence, of low or very low quality, to suggest that intake of SDS, as wholegrains, reduces risk of oral cancer and of periodontitis**.** To our knowledge this is the first systematic review assessing the impact of starch on oral health; a scoping review and search on PROSPERO did not reveal any previous systematic review of the impact of starch, or of replacing RDS with SDS on oral health**.**

This systematic review has identified low/very low quality evidence pertaining to starch intake and oral health which largely reflects the observational nature of the data. The GRADE method classifies observational studies as 'low quality' and upgrading to a higher level is dependent on evidence of a large effect size, a dose response or if confounders are likely to minimise the effect (e.g. when the estimated effect is based on data from only unhealthier people, exposed to a product, the actual effects may be greater than suggested (WHO 2014)). Moreover, observational data can be downgraded to 'very low' quality if there is risk of bias (e.g. due to confounding), imprecision, inconsistency of results, indirectness, or if publication bias is likely.

Dental caries

The UK Scientific Advisory Committee on Nutrition (SACN (2012) concluded there was a lack of data pertaining to total starch intake and caries, however, this conclusion was based on a lack of RCTs and one identified cohort study (Rugg-Gunn et al. 1987). The current review took a more holistic 'best available evidence' approach and found consistent, albeit low quality, evidence from 4 cohort studies that showed no association between total starch and caries risk.

The current review also found 'low quality' epidemiological and experimental data to suggest that RDS starches may increase risk of caries. Most experimental studies did not directly compare RDS with SDS, however, the form of starch tested was usually RDS. Oral bacteria do not metabolise starch per se but it is plausible for starch to be cariogenic if hydrolysed to sugars intraorally by amylase. The experimental data indicated that RDS can lower pH and cause demineralisation if retained in the mouth long enough for hydrolysis to occur (i.e. >45 minutes). This suggests that for RDS, oral retentiveness (e.g. food sticking to or trapped between teeth) is important in determining the cariogenic potential.

Oral cancer

Despite evidence from the meta-analysis of a protective effect of SDS and an adverse effect of RDS, the amount of evidence pertaining to starch intake and oral cancer was limited and diverse; results need to be interpreted with caution. Meta-analysis for SDS was limited to data from two cohort studies on the impact of wholegrains, on adult females from the US, one including post-menopausal women only. Moreover, there were differences in the classification of cancers and quantification of SDS (Table 4). With respect to data pertaining to RDS, the confidence intervals for the overall estimate were wide and there was heterogeneity between studies with respect to classification of types and amounts of starch intake. Moreover, Chatenoud et al. (1999) included oesophageal and laryngeal cancers in addition to oral and pharyngeal cancers. It is therefore not possible to draw any firm conclusions. Despite the inclusion of data from 5 more recent studies, the findings concur with the WCRF second expert report on diet and cancers that concluded the data on starchy foods and oral cancer were either of too low quality, too inconsistent, or the number of studies too few to draw conclusions (Hartman et al. 2006).

Periodontal disease

The small amount of low quality data pertaining to starch type and risk of periodontitis, precludes the formation of any firm conclusions. Any protective effect of wholegrains may be associated with component antioxidants; as previous research has shown antioxidant nutrients to have a mitigating effect (Chapple 1997).

Limitations

Because of different reporting standards in studies, only odds/hazards ratio and 95% confidence intervals could be used to inform the meta-analysis. The overarching effect estimates generated by meta-analysis need to be read and interpreted with caution. The forest plots (see Appendix) provided an overview of the possible direction of evidence as opposed to being conclusive.

Due to small number of comparable studies of similar design across the respective oral health outcomes, it was not feasible to conduct sub-group or sensitivity analysis, determine dose response or threshold effects, or assess publication bias through funnel plots.

Classification of dietary starch

To minimise risk of diet-related diseases, most dietary guidelines promote a high percentage of energy intake from carbohydrate preferably as starch in the form of wholegrains or as fruits and vegetables (Nishida et al. 2004; SACN 2015; USDA 2015). Starch is heterogeneous in nature: it may be consumed cooked, with sugars (e.g. biscuits, cake, breakfast cereals) or without sugars (e.g. pasta, oatmeal) or raw (e.g. in fruits and vegetables) and varies in degree of processing, from unprocessed to highly refined. There is currently only one well-defined classification for distinction of RDS vs. SDS (Cummings & Stephen 2007) but data on RDS, SDS and resistant starch in food compositional tables for use in dietary epidemiological studies are lacking. The approach to classify starch type used in this paper included a number of different ways to distinguish RDS and SDS, e.g. lower versus higher legume intakes; highly processed versus less processed starch foods; refined carbohydrate compared with wholegrain carbohydrate; and carbohydrates with higher compared with lower glycaemic response. However, the majority of data pertaining to risk of oral cancer and of periodontal disease related to the impact of increased intake of wholegrains suggesting a protective effect. Data from some experimental studies, on proxies for caries, also enabled comparisons of wholegrain vs. non-wholegrain and suggested wholegrain foods to have lesser cariogenic potential (Appendix Table 15). Available epidemiological data on dental caries related only to the impact of starch that could be classified as rapidly digestible.

The UK SACN (2015) found no evidence of an association between total starch intake and risk of coronary events or diabetes but concluded there was insufficient evidence pertaining to starch and CVD or weight gain. However, when assessing the impact of carbohydrates on health it may be more appropriate to consider wholegrain vs. non-wholegrain starches. When conducting dietary surveillance and when providing dietary advice, there is a need to distinguish less healthy types/sources of starch (i.e. highly processed) from the healthier forms/foods. Carbohydrates are an important source of dietary energy and dental professionals should not recommend restricting total carbohydrate. Promoting carbohydrates from wholegrain cereals, fruits and vegetables and whilst restricting other forms, is likely to protect oral as well as systemic health.

Future research

Starch, by virtue of being a diverse food group, needs to be more clearly defined in future research. A number of studies had to be excluded for this review as they failed to provide an adequate measure of starch. Even in the included studies, classifications of starch were sometimes vague or difficult to distinguish from other food items/nutrients (e.g. sugars). Starches need to feature in future research with the intention that separate impacts on oral health outcomes can be isolated. Additionally, making conclusions on the ideal amount of starch/starch type is not possible based on the current findings, as studies differed or did not specify the amount of starch intake that was considered for different intake categories (e.g. 'high' intake). Higher quality studies need to be designed and implemented to enable firm conclusions to be drawn regarding any relationship between different types of starch/starch rich foods (e.g. wholegrain vs. non-wholegrain) on oral cancer and on periodontal disease and to confirm the current observations pertaining to risk of dental caries.

Conclusions

This systematic review shows evidence that intake of RDS but not total starch intake is associated with increased risk of caries. There is limited evidence suggesting wholegrains may protect against oral cancers. In line with advice for general health, dental health professionals should promote consumption of SDS such as that found in wholegrains, fruits and vegetables and advocate limiting RDS only, especially when combined with free sugars.

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Table 1 Questions Posed by the WHO Nutrition Guidance Expert Advisory Group – Subgroup on Diet and Health, to Develop Recommendations Regarding Starch Intake

Question
1. What is the effect of an increase in intake of slowly digestible starch on oral health?
2. What is the effect of an increase in intake of rapidly digestible starch on oral health?
3. What is the effect of a decrease in intake of slowly digestible starch on oral health?
4. What is the effect of a decrease in intake of rapidly digestible starch on oral health?
5. What is the effect of an increase in intake of total starch on oral health?
6. What is the effect of a decrease in intake of total starch on oral health?

Table 2. Summary of included studies on dental caries

Study	Country	Starch	Starch Measure	Oral Outcome	+ / 0 / - /n/a*	n	Age	Comment
Total Starch								
Non-randomised intervention								
Scheinin and Mäkinen 1975	Finland	Xylitol, fructose and sucrose groups where starch intake was not restricted but remained constant	n/a	Dental caries (increment)	n/a	125	<15-≥45	Large caries increase in sucrose group compared to xylitol
Cohort studies								
Marshall et al. (2005)	USA	Starches (general food types e.g. bread, cereals)	Annual 3 day diet diaries	Dental caries	0	398	1-6.8	Higher--income families
Campain et al. (2003)	Australia	Low sugar-high starch diet	Online diet records	Dental caries	0	645	12-13	-
Rugg-Gunn et al. (1987)	England	High-starch/low-sugar diet	Annual 3 day diet diaries	Dental caries (increment)	0	405	12-14	-
Kaye et al (2015)	USA	Dietary Approaches to Stop Hypertension (DASH) adherence score and intake of starch	FFQ	Root caries (increment)	0	533	47-90	Males only
Cross-sectional								
Arcella et al (2002)	Italy	Low sugars/high starch, high sugars/high starch	14 day diet diaries	Dental caries	n/a	193	13-17	Suggests increased risk when starch combined with sugars
Papas et al (1995)	USA	Mean frequency of exposure to various categories of food, including e.g. ‘starches’, ‘sugars and starches’	FFQ	Root caries	n/a	275	44-64	Suggests increased risk when starch combined with sugars

Ecological								
Holloway et al (1963)	Tristan da Cunha islanders examined in the UK	Changes to diet consisting mainly of potatoes, introduction of sugars etc.	Ecological study into islanders' diet	Dental caries	n/a	167	1-49	Suggests increased risk when starch combined with sugars
Fisher (1968)	Tristan da Cunha (British Overseas Territory)	Changes to diet consisting mainly of potatoes, introduction of sugars etc.	Ecological study into islanders' diet	Dental caries	n/a	149	1-49	Suggests increased risk when starch combined with sugars

Study	Country	Starch	Starch Measure	Oral Outcome	+ / 0 / -*	n	Age	Comment
RDS vs. SDS *Cohort studies*								
Chankanka et al. (2011)	USA	Unprocessed (SDS) and processed starches (RDS)	Multiple 3 day food diaries	New cavitated carious lesions	Processed starches at snacktime (+*), Unprocessed starches (0*)	198	5	
Campain et al. (2003)	Australia	Low sugar-high starch	Multiple 4 day food diaries	Dental caries	+	645	12-13	
Cross-sectional								
Llena and Forner (2008)	Spain	Foods rich in semi-hydrolysed starch	FFQ	Dental caries	+	369	6-10	-
Ecological								
Sreebny (1983)	47 nations	Wheat, rice and maize	National cereals supply data	Dental caries	Wheat (+), rice (0) and maize (-)	47 nations	12	-

* '+' signifies a positive and significant relationship between intake of the particular starch item and dental caries (i.e. higher intakes are associated with increased risk), while '**0**' signifies no significant relationship and '**-**' signifies a negative and significant relationship between intake of the particular starch item and dental caries (i.e. higher intakes are associated with reduced risk), 'n/a' signifies no result for the outcome for isolated starch as this was combined with sugars

*At $p<0.10$ significance level

Table 3 Summary of included studies on oral cancer

Study	Country	Starch	Starch Measure	Oral Outcome	+ / 0 / - *	n	Age	Comment
Total Starch								
Case-control								
Bravi et al. 2013	Italy and Switzerland	Starch (g)	FFQ	Oral and pharyngeal cancer	0	2,846	19-79	-
RDS vs. SDS								
Cohort studies								
Kasum et al. 2002	USA	Whole-grain (SDS)	FFQ	Upper aerodigestive cancer	-	34,351	55-69	Restricted to postmenopausal women
Lam et al. 2011	USA	Whole-grain (SDS)	FFQ	Head and neck cancer	-	494,991	50-71	-
Case-control								
Bosetti et al. 2000	Italy and Switzerland	Whole-grain (SDS)	Questionnaire	Oral and pharyngeal cancer	0	671	<45-≥65	Restricted to female population
Aune et al. 2009	Uruguay	Legumes (SDS)	FFQ	Oral and pharyngeal cancer	-	2315	23-89	-
Giraldi et al. 2016	Italy	Legumes (SDS)	FFQ	Head and neck cancer	-	933	<60-≥70	-
McLaughlin et al. 1988	USA	Legumes (SDS)	Questionnaire	Oral and pharyngeal cancer	0	1,850	18-79	Restricted to Caucasian sample
Chen et al. 2016	China	Beans (SDS)	Questionnaire	Oral cancer	0	888	20-85	Restricted to male population
Chatenoud et al. 1999	Italy	Refined grain (RDS)	Questionnaire	Oral, pharyngeal, laryngeal and oesophageal cancer	+	4,109	Younger than 75	-
Levi et al. 2000	Switzerland	Refined grain (RDS), whole-grain (SDS)	FFQ	Oral and pharyngeal cancer	Refined grain (+), whole-grain (0)	505	34-74	-

Figure: Flow Chart of Searches and Screening.

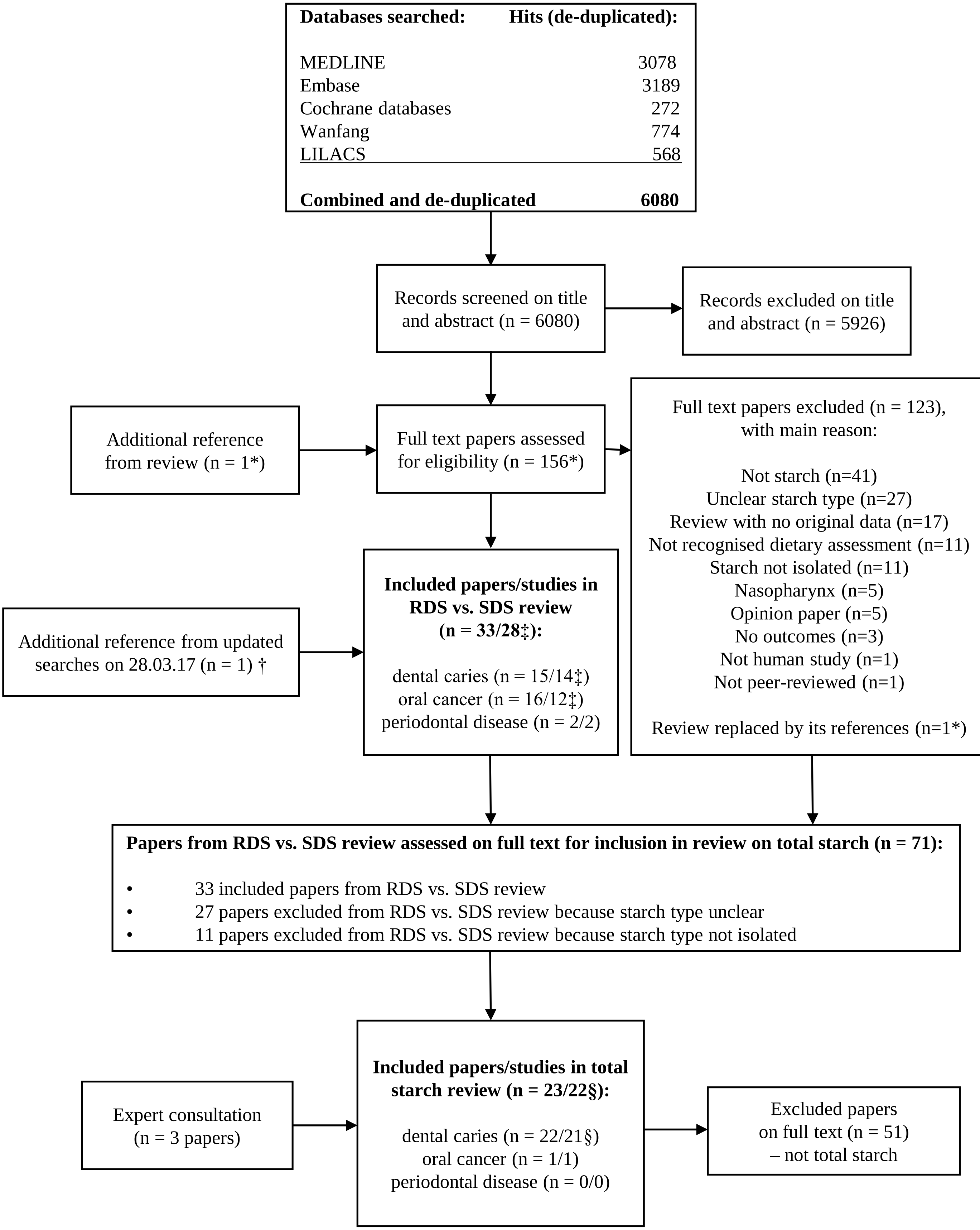

Figure. Flow chart of searches and screening.

* One reference only, on oral cancer, was identified from a systematic review of cancers was included and review excluded.

† Updated searches were conducted on the 28.03.2017

‡ Of the 15 papers on dental caries, only 14 studies were considered as two of the papers consisted of overlapping samples (Marshall et al., 2005; Chankanka et al., 2011) only the most recent analysis (Chankanka et al., 2011) was included. Of the 16 papers on oral cancer, only 12 studies were synthesised as 5 papers consisted of overlapping samples (De Stefani et al., 1999; De Stefani et al., 2000; De Stefani et al., 2005; Aune et al., 2009; De Stefani et al., 2013). Only the most comprehensive analysis (Aune et al., 2009) was included.

§ Of the 22 included papers on dental caries, only 21 studies were considered in the evidence synthesis due overlapping samples (Mariri et al., 2003; Marshall et al., 2005). Only the most comprehensive analysis (Marshall et al., 2005) was used in the evidence synthesis.