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Review article

Long-term (10-year) dental implant survival: A systematic review and sensitivity meta-analysis

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ABSTRACT

Objectives: To identify and appraise the most recent studies reporting dental implant survival in adults (≥18 years) using contemporary implant systems (solid screw, roughened surface) for a period of 10 years; and explore new predictors of implant survival.
Source: MEDLINE, Scopus, and the Cochrane Central Register of Controlled trials were searched from 1997 to January 2018 to focus on contemporary implant systems.
Study selection: Only prospective observational studies with at least 10 participants and 35 implants were included. The unit of study was the ‘absolute survival’ rate of dental implants after 10 years in the oral cavity. Study quality was assessed utilising a modified Hoy risk of bias tool for prevalence studies. A sensitivity meta-analysis was undertaken utilising a plausibly imputed model for missing data.
Data: 18 studies met the inclusion criteria. The summary estimate for 10-year survival at the implant level was 96.4% (95% CI 95.2%–97.5%) and the prediction interval was 91.5%–99.4%. The sensitivity meta-analysis summary estimate of survival was 93.2% (95% CI 90.1% to 95.8%)$p = 0.041$ with a prediction interval of 76.6%–100%. Older age (≥ 65 years) was a significant predictor at 91.5%, $p = 0.038$ in the sensitivity meta-analysis.
Conclusions: A traditional analysis produced similar 10-year survival estimates to previous systematic reviews. A more realistic sensitivity meta-analysis accounting for loss to follow-up data and the calculation of prediction intervals demonstrated a possible doubling of the risk of implant loss in the older age groups.
Clinical significance: Improved analysis provides the clinician with better estimation of the real-world risk of implant failures so helping the clinician communicate the potential risk to patients.

1. Introduction

1.1. Rationale

Titanium dental implants have been in use for over 50 years and according to the literature [1,2] are a highly successful treatment option for the long-term (10-years plus) replacement of missing teeth. In clinical dental practice there are concerns as to whether this success rate is achievable in the general population of suitable dental patients [3] and whether it should be `used to guide clinical decision making. A paper from the United States collected data from general dental practices involved in the Practitioners Engaged in Applied Research and Learning (PEARL) network [4]. They followed up 922 implants over a mean follow-up time of 4 years and based their results on two classifications of implant failure; implants physically lost from the oral cavity resulted in a survival rate was of 93.0% (95% CI: 91.4 to 94.7); if they included excessive bone loss around the implant in their failure criteria [2] the result dropped significantly to 81.3% (95%CI: 78.8 to 83.8) $p \leq 0.01$. Da Silva’s most optimistic practice-based results were significantly lower ($p \leq 0.01$) than the 5-year survival data from academic research 95.6 (95%CI: 94.4 to 96.6) [5].

To assess the current situation seven major systematic reviews assessing the long-term survival of dental implants [5–11] were appraised. The authors of these reviews broadly defined survival as “the implant remaining in situ at the follow-up examination”. The conclusions in Pjetursson’s 2004 and 2012 reviews [5,11] gave 10-year

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Table 1
Summary of previous systematic reviews.

Systematic Review First author and year of publication	Affiliation	Number of studies (10-years)	Earliest study	Superstructures	10-years survival % (95% CI)	Number of implants	Published protocol (type/registered)	Included observational studies	Risk of Bias tool	Missing data analysis
Pjetursson et al. 2004	Bern Switzerland	6 (1 RCT)	1997	Fixed partial denture	92.8 (90.0 to 94.8)	804	No/No	Combined	No	No
Jung et al. 2012	Zurich Switzerland	4 6	1999	Single crown Single crown	94.9 (88.7 to 97.5) 95.3 (90.2 to 97.8)	124 267	No/No	Prospective Retrospective	No	No
Pjetursson et al. 2012	Reykjavik Iceland	6	1997	Fixed dental prosthesis	92.8 (90.0 to 94.8)	804	No/No	Prospective	No	No
		1 (1 RCT)		Fixed dental prosthesis	94.8 (89.7 to 97.9	69		Retrospective		
Papaspyridakos et al 2014	Athens Greece	1	2005	Fixed complete prosthesis	96.9 (96.0 to 97.7) (rough surface)	90	No/No	Prospective	Yes (NOS)**	No
		1			97.9 (96.8 to 99.0) (smooth surface)	194				
Moraschini et al. 2015	Niterói Brazil	10 (1 RCT)	1999	Single crown, Fixed dental prosthesis, Fixed complete prosthesis, Overdenture	96.5 (90.3 to100)	1435	PRISMA §/No	Combined	Yes (Needleman) (Cochrane) ††	No
Hjalmarsson et al. 2016	Göteborg Sweden	9	2001	Single crown	95.0 (91.8 to 100)	527	No/No	Combined	No	No
Srinivasan et al. 2016†	Geneva Switzerland	3	2012	Single crowns Overdenture	91.2 (83.4 to 95.6) 80.5 (45.5 to 95.3) ‡	101	PRISMA/No	Prospective	Yes (NOS) (Cochrane)	No Yes

† = Limited to elderly population > 65 years old.
‡ = All lost to followup considered a failure.
§ = PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis).
**= Newcastle Ottawa Scale.
†† = Cochrane Collaboration's tool for assessing risk of bias in randomised trials.

implant survival as 92.8% (95% CI:90 to 94.8) and 93.1% (95% CI: 90.5 to 95.0) respectively based on 6 prospective studies with a median of 81.5 implants per study. A more recent systematic review [12] increased the 10-year survival rate to 95% (95% CI: 91.8 to 100.0). There are several points to note from the systematic review data presented in Table 1.

Most of the systematic reviews are associated with European universities (no large systematic reviews were from North America or Asia). There is robust evidence to support the co-location of business research and development (pharmaceutical and medical devices) with relevant university research departments [13] and an associated increased risk of bias [14].

There are few prospective studies included in these reviews making their findings dependent on retrospective studies which are vulnerable to selection bias [15].

All but one review [8] included studies which started in the 1980s. Many of the dental implants used in the studies cited in the earlier reviews have been superseded or discontinued (turned metal surface and hollow cylinders) and therefore their survival data does not directly apply to contemporary clinical practice [16–18].

Only two studies used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19] template and Cochrane Handbook for Systematic Reviews of Interventions [20] to develop their protocols and select quality and risk of bias tools. In a recent review regarding the impact of PRISMA there was only approximately 20% uptake in registration of a protocol, and 55%–60% uptake in undertaking a 'risk of bias' analysis[21].

One feature of long-term survival data is its susceptibility to losing patients to final assessment, referred to as attrition. Studies missing more than 20% follow-up data may be vulnerable to a higher risk of bias in their results [22], especially if the loss to follow-up is not 'at random' i.e. loss is related to implant failure. In the two most recent reviews [7,8] only one study per review had complete data to analyse, with a maximum lost to follow-up (LTFU) of 45.5%. All the reviews assumed the data was 'missing at random' and therefore unbiased, the results were then produced using a 'complete case analysis' model for their primary outcome. In the main text of the primary papers the LTFU patients were usually categorised as: moved away (8%); died (25%); ill health (8%); unspecified technical issues (9%), leaving 50% of the missing patients uncategorised.

1.2. Aims and objectives

The aim of this systematic review was to assess the effect on published 10-year survival estimates of contemporary changes in implant design and placement, and new data analysis techniques.

The participants, interventions, comparators and outcomes (PICO) for this review were:

P - Adults humans ≥ 18 years old.

I - Titanium roughened surface solid screw dental implants replacing missing teeth.

C - No comparator (the review is looking at absolute implant survival).

O – 10-year survival of the implant

2. Materials and methods

2.1. Protocol and registration

The protocol, abstract and review were developed in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis framework [23] and details of the protocol for this systematic review were registered on the International Prospective Register of Systematic Reviews (PROSPERO) Reg. No: CRD42017072765 and can be accessed at www.crd.york.ac.uk/PROSPERO /display_record.asp?ID = CRD42017072765.

2.2. Eligibility criteria

2.2.1. Study designs

Eligible studies included randomised controlled trials, non-randomised or pseudo-randomised clinical trials and prospective cohort designs. Within these studies the unit of study was only the implant survival component. Studies had to have at least 10 participants and a minimum of 35 implants to reduce the impact of small case-studies. All the studies were quantitative. The search inception date was from the 1 st January 1997 to 1 st January 2018 as this would optimise the number of studies whilst reducing the inclusion of early turner or hollow implant systems from the mid-1960s to late 1990s (i.e. Brånemark Mk II).

2.2.2. Participants

The studies examined healthy adult humans (18 years or older) who had some or all their natural teeth missing and were subsequently restored using titanium dental implants.

Excluded were patients diagnosed with bisphosphonate related osteonecrosis of the jaw [24]; patients with implants placed in irradiated bone or with major vertical bone grafting [25]; patients having maxillofacial reconstruction following oncology or major facial trauma, as it was presumed these groups would mainly be treated in a hospital environment

2.2.3. Interventions

These included restorations comprising of two-piece, micro-roughened surface, solid screw, pure titanium or titanium alloy dental implants supporting single crowns, implant supported fixed partial dental prosthesis, implant supported full arch prostheses and removable implant supported over-dentures. Obsolete and novel/prototype implant systems were excluded, examples being:

- Turned-surface or hollow cylinder implants, these implants were gradually superseded by rough surface implants which exhibited greater bone healing and higher quality osseointigration but dominated many of the studies between 1965–1997. There is insufficient data to conclude that implant surface had any significant effect on the development of peri-implantitis [26,27]. These implants have been excluded due to a lack of current commercial availability.
- Hydroxyapatite coated, non-titanium (zirconium) or novel implant systems [28].
- Implants less than 3 mm in diameter or 6 mm long as they are recommended for use in limited situation [29,30].

2.2.4. Setting

There were no restrictions on the type of setting

2.2.5. Information sources

Having consulted with a Health Sciences Librarian, MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), 1946 to present), Scopus (Elsevier), and the Cochrane Central Register of Controlled trials (CENTRAL) (Wiley Online Library) were searched. To ensure literature saturation relevant journals were identified and searched in the field. In the final stages of the electronic search the journals were hand searched, including PROSPERO and the grey literature (www.opengrey.eu) for any additional studies. There were no language restrictions.

2.2.6. Search strategy

Specific database search strategies were created and tested. To balance yield with precision it was necessary to use terms set for maximum sensitivity to allow for errors in indexing, and inconsistencies in the descriptions of studies which would otherwise make them difficult to locate [31,32]. The final MEDLINE strategy was adapted to the syntax and subject headings of the other databases. The search strategy

Table 2
MEDLINE search - Ovid interface.

	Keyword	Search results
1	Exp Dental Implants/	19,075
2	((tooth or teeth or dental) and (implant* or osseointegrat*)).ti,ab.	21,218
3	1 or 2	303,825
4		1,243,308
5	(10 year* or ten year*).af.	168.961
6	3 and 4 and 5	320
7	exp animals/ not humans.sh.	4,397,076
8		319
9	**limit 8 to yr="1997 -Current"**	**299**

applied to all databases mentioned and used a combination of terms similar those used in Table 2.

2.2.7. Study records

2.2.7.1. Data management. Literature search results were uploaded to Covidence systematic review software (https://www.covidence.org).

2.2.7.2. Selection process. Two independent reviewers (M–S.H, W.K) screened the titles and abstracts from the search against the inclusion criteria. Full reports were obtained for titles that fulfilled the inclusion criteria. Study authors were to be contacted if additional information was necessary for clarification. Any disagreements were resolved by discussion with a third party (D.R).The reasons for excluding any studies were recorded.

2.2.8. Data items

The predefined data from the included studies was extracted and the second reviewer checked the data for accuracy. Disagreements were resolved by discussion between the three reviewers.

Information was extracted on study identification data, and the characteristics of the studies (participants, implants numbers and types, superstructure and summary data etc.).

2.2.9. Data assumptions

- Where studies consisted of multiple treatment groups such as different types of implant superstructure, the groups were combined into a single group to analyse ‘absolute’ survival of the implants only. This also applied to location of the implants in the maxilla or mandible as the position of the implants lost was not defined consistently in all the studies.
- For the imputed data an alternative method of addressing missing individuals originally proposed by Akl was applied [33,34]. The main assumption being that there is a relatively higher number of adverse events in the patients LTFU. For the purposes of this review the Relative Event Incidence ($REI_{LTFU/FU}$) is the ratio of LTFU failure rate over those followed-up (FU). Using the available evidence Akl recommended that if the LTFU were unknown then the $REI_{LTFU/FU}$ should be set at a 5-time greater failure rate in the LTFU group as it represented the highest evidence-based value reported of missing data that had been actively followed-up.
- In several of the primary studies the authors mention the number of patients LTFU but omitted the number of implants attributed to those patients. The mean number of implants per patient at the beginning of the study was used to estimate the number of implants in the LTFU group.
- It was unclear within the primary studies as to specific age groups receiving implants (mean plus range). In line with a previous systematic review which defined an elderly population as greater than 65 years old it was possible to divide the eligible studies into two groups[8]. One group had an age range from 18 to 64, and a second group which ranged from 18 to ≥65 years.

2.3. Outcomes

2.3.1. Primary outcomes

To establish of the survival rate of two-piece, micro-roughened surface, solid-screw, titanium dental implants in the oral cavity presented as a proportion of the total number of dental implants remaining in the oral cavity after 10-years. Implant failure was defined according to the criteria specified in the individual studies (lost from the oral cavity), as was LTFU (complete case analysis).

2.3.2. Secondary outcomes

To create a dataset for sensitivity meta-analysis based on the proportions of implant survival and implant failure (1-proportion survival) at 10-years calculated using plausible imputation of missing data earlier defined [33] and implant failure was defined as an implant fulfilling at least one of the criteria in Group IV of the International Congress of Oral Implantologists (ICOI) Pisa Implant Quality of Health Scale [35] to allow for those implants that have technically failed but have not been lost from the oral cavity.

2.4. Risk of bias in individual studies

Two reviewers (M–S.H, W.K) assessed risk of bias (RoB) using a tool specifically for assessing prevalence developed by Hoy and colleagues [36]

2.5. Data synthesis

Historically heterogeneity has been relatively high in dental studies [37] either clinically (implant type, surgical technique, type of tooth loss, population type and number) or methodologically (different study designs, review periods, retrospective database analysis) leading to statistical variation. In a conservative approach, to account for the ‘between studies’ heterogeneity in the effect sizes, the meta-analysis was undertaken using a random effects model (DerSimonian-Laird estimator for τ^2) [38], Freeman-Tukey double arcsine transformation [39] for handling proportions close to the 0 and 1 values [40], and Clopper-Pearson confidence interval for individual studies [41,42].

2.5.1. Measurement of treatment effect

The dichotomous data was presented as the survival rate (SR) of implants in situ (IS). In the sensitivity analysis the implants in situ fulfilled PISA criteria 1–3 at the 10-year clinical assessment. The proportion surviving was calculated by dividing the IS implants by the total number of implants placed at the initiation of the study (II), expressed as a percentage. (SR = (IS/II) *100). The relative risk ratio was used to compare the ‘complete case’ meta-analysis with the ‘imputed’ outcome. The confidence interval for the survival proportions were calculated by using the 95% confidence limits of the event rates.

2.5.2. Unit of analysis

The unit of analysis was the dental implant. Most of the studies did not specifically define this in their methods/results sections as their primary outcome was some other area of study such as restoration type or surgical technique. To standardise the inclusion criteria, the minimum standard of survival required only that the implant remained functional in the oral cavity at the 10-year evaluation point for the primary outcome.

2.5.3. Assessment of heterogeneity

Heterogeneity was tested using the I^2 statistic as high levels of heterogeneity among the trials existed ($I^2 \geq 50\%$ or $P < 0.1$), the study design and characteristics in the included studies were analysed via subgroup and sensitivity analysis.

2.6. Synthesis of results

Each outcome was combined and calculated using the statistical packages 'meta' [43] for meta-analysis and 'metareg' [44] for meta-regression within the statistical software environment R. Survival rates were combined using the 'metaprop' package and graphically displayed in a forest plot. Prediction intervals were calculated to describe the distribution of true effects around the summary effect [45]. A random effects model was used in the meta-analysis to incorporate variability in true effects across the studies [46].

2.6.1. Sensitivity analysis

A standard sensitivity analysis was performed to explore the source of heterogeneity associated with the imputed missing data, and risk of bias (by omitting studies that are judged to be at high risk of bias) within the studies.

2.6.2. Subgroup analysis and meta-regression

Subgroup analysis was carried out for the complete case and imputed meta-analysis results. The relative risk ratio (RRR) was used to compare the difference in risk between the 'imputed' and the 'complete case' sensitivity meta-analysis results (RRR = $p_{\text{imputed}} / p_{\text{complete case}}$) in terms of survival and failure (1-proportion survival). Subgroup analysis was used for categorical data. The subgroups were:

- Age (divided into two groups; patients aged 18–64 years and 18 to ≥ 65 years).
- Implant by manufacturer (Straumann, Nobel BioCare (Brånemark), Dentsply(Astra), Friadent, Sweden & Martina, Biomet 3i)
- Superstructure type (single crowns, fixed bridges, full arch reconstructions and over-dentures)
- Bone augmentation (whether localised bone regeneration techniques were utilised at the time of implant placement).

Meta-regression was calculated for continuous data:

- Age (mean)
- Patient drop-out

2.6.3. Publication bias

The data was analysed both graphically with a funnel plot, and statistically using Egger's Test [46] for both the complete case and imputed results to compare the effects.

2.6.4. Confidence in cumulative estimate

The quality of evidence for all outcomes was judged using GRADE (Grading of Recommendations Assessment, Development and Evaluation working group methodology) [47,48]. GRADE certainty ratings cover the subjective domains of risk of bias, imprecision, inconsistency, indirectness and publication bias.

3. Results

3.1. Study selection

The search of Medline, Scopus and Cochrane Central Register of Controlled Trials provided a total of 847 citations. After removing duplicated titles and abstracts 567 remained for screening. Of these, 477 were discarded because after reviewing the abstracts they did not meet the inclusion criteria. The remaining 90 full-text articles were assessed for eligibility. Three studies were immediately discarded as full text for the study was not available for download. The full-text of the remaining 87 citations were examined, 69 did not meet the inclusion criteria and were excluded. A detailed flow diagram of literature retrieval is shown in Fig. 1.

3.2. Study characteristics

Of the 18 studies included in the meta-analysis 4 were described as RCTs (three assessed implant superstructures, one assessed time of implant placement) [49–52], and 14 as prospective cohort studies [53–66]. The setting for 15 of the studies was in a university teaching hospital and 3 in private specialist practice. The number of patients ranged from 12 to 250 with a median of 42, and the number of implants ranged from 35 to 506 with a median of 119. Funding source was not disclosed in 14 studies, 3 were part funded by industry [49,52,63] and 1 by the State [57]. The earliest start date for the studies was 1992 (the start of the contemporary implant designs) and the latest 2006. The median age of subjects involved in the studies was 51 years, ranging from a minimum of 15 years to a maximum of 84 years; 2 subjects were less than 18 years old and following discussion would have a minimal effect on the pooled result so the two studies were not excluded [55,56]. All the studies classed their patients as healthy and 16 out of the 18 studies included patients who smoked tobacco products. There were 7 different implant systems used; Biomet 3i, Nobel Biocare Brånemark, Straumann, Sweden & Martina, Friadent Dentsply, Astra Dentsply and Southern. Three studies included localised bone augmentation (repair) with either a bovine material (BioOss, Geistlich Pharma AG, Switzerland) by itself or mixed with autogenous bone. Regarding the superstructure placed on the implants 46% were single crowns, 40% fixed partial prostheses, 8% overdentures and 7% fixed full arch prostheses. The mean percentage LTFU for patients was 20% after 10 years ranging from 0 to 73 patients depending on the study. Only 22% of the studies in this review had no missing data and all restricted analysis to participants with full outcome information. The data providing a reason for the LTFU was divided up into; patient died 10.5%; too sick to attend 5.2%; moved away 5.2% and, failed to attend/uncategorised 79.1% [49–51,53–67] (see Tables 3 and 4).

3.3. Risk of bias within studies

The consensus judgements regarding the 10 domains of bias and the overall risk of bias assessments for the studies are detailed in Table 5. The studies with the highest risk of bias were [52,55,58,61,63].

3.4. Synthesis of results

Two meta-scenarios were distinguished

3.4.1. Primary outcome meta-analysis

The primary scenario included 2688 implants of which 98 were lost. The summary estimate for the complete case analysis group was 96.4% (95% CI: 0.95% - 0.98%) with moderate heterogeneity (I^2 = 54% p = < 0.01), the predictive interval suggests that the true effects lie between 92%–99% (see Fig. 2).

3.4.2. Sensitivity meta-analysis

The second scenario, with the additional imputed data included 2701 implants of which 199 were lost. The summary survival estimate proportion was 93.2% (95% CI: 90%–96%), with very high heterogeneity (I^2 = 87%, p = < 0.01) and a wider predictive interval of 77%–100% (see Fig. 3).

3.4.3. Sensitivity and subgroup analysis for primary outcome

None of the pre-planned subgroup analyses by age, manufacturer, bone augmentation or LTFU rate of ≥ 20% were statistically significant. There was no statistically significant difference if the highest risk of bias studies were excluded from the meta-analysis.

3.4.4. Sensitivity analysis between scenarios

When the two scenarios (complete case vs. imputed data) were compared there was a statistically significant drop in implant survival

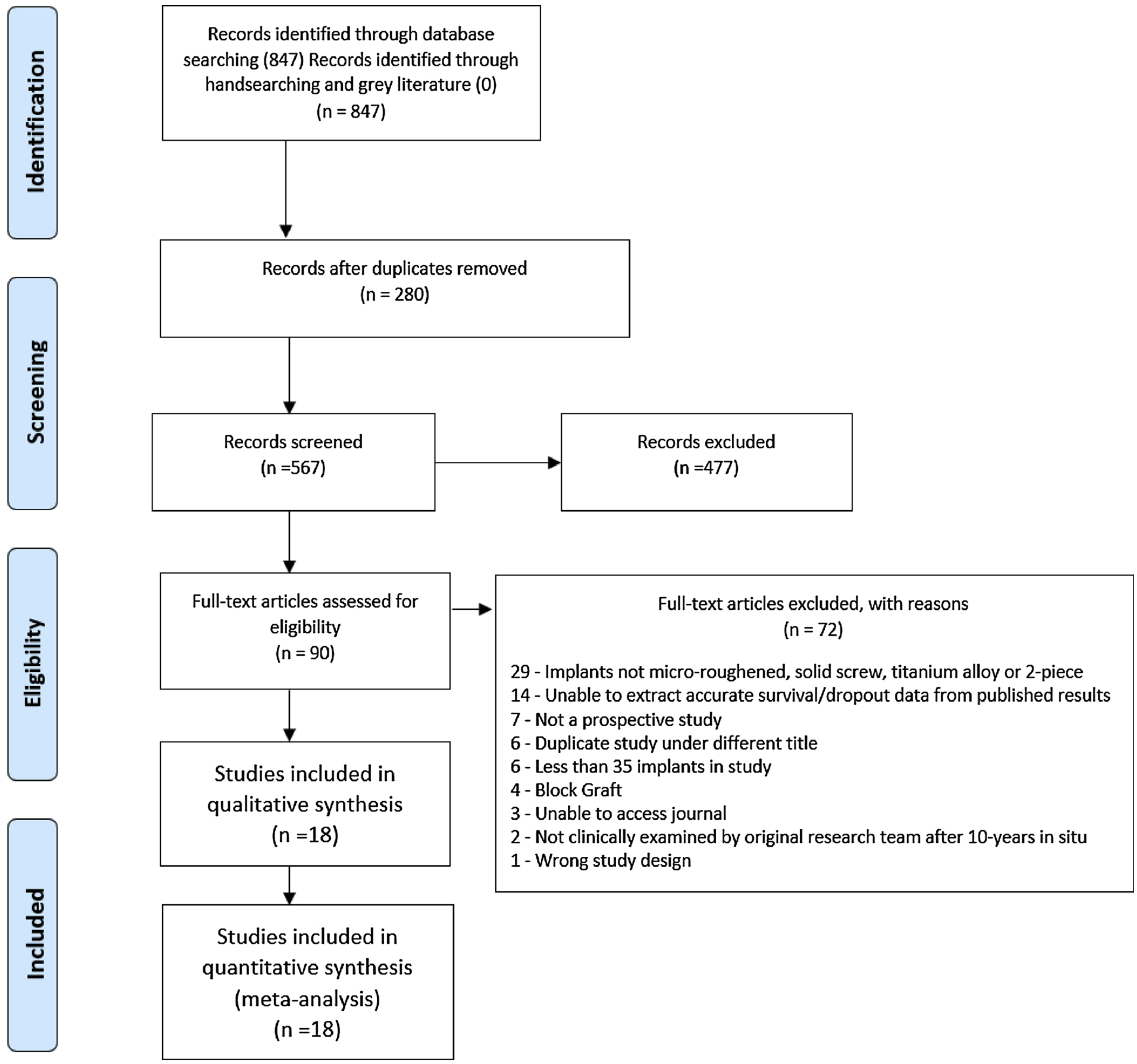


Fig. 1. Flowchart of the search process.

for the imputed data group. The three subgroups; maximum age ≥65 years, LTFU ≥ 20%, superstructure (specifically overdenture) and the high risk of bias group showed increased risk ratios for implant failure but not for survival. There were no significant differences between manufacturer or bone augmentation (see Table 6).

Meta-regression was carried out on patient LTFU and age group. There was a statistically significant reduction in implant survival of 0.6% for every 1% of patients LTFU in the imputed data group but no significant association in the complete case group. For the binary variable 'age group' there was no difference in either scenario.

3.5. Risk of bias across studies

3.5.1. Publication bias

The funnel plot shows the changes in symmetry between the complete case (A) and imputed meta-analysis (B). To confirm the differences the results of the Egger's test was based on the null hypothesis of 'no bias in the meta-analysis'. From the test statistics and funnel plots the null hypothesis for the imputed data group ($p = 0.56$) could not be rejected. In the complete case data group the test statistic was significant ($p < 0.05$) suggesting increased risk of publication bias (see Fig. 4).

3.6. Confidence in the cumulative estimate

The summary of evidence quality across studies (GRADE) was very low. Even though the studies were all prospective with moderate clinical heterogeneity they were vulnerable to selection bias from high heterogeneity in methodology and missing data (see Table 7).

4. Discussion

4.1. Summary of key findings

Following conventional protocols employed in earlier reviews of 10-year implant survival the summary estimate of 96.4% (95% CI: 95% - 98%) demonstrates a small non-significant improvement in survival with the narrowing of the confidence intervals [5]. The associated prediction interval ranged from 92% to 99%. The subgroup analysis and meta-regression showed no significant differences. The only exception was implant supported maxillary overdentures which produce a significantly lower survival rate mirroring the results of an earlier study of 87.3% for 10-year cumulative survival [68].The sensitivity test created by excluding the high risk of bias studies showed no statistically significant difference. Publication bias was revealed by an asymmetry

Table 3
Summary of included studies evaluation long term implant survival.

Study			Patients			Follow-up		Implant system	Clinical setting
Author (year)	Study start (Year)	Study design	Number	Mean age (years) Age range (min, max)	Sex (M, F)	Lost to follow-up (%)	Patients (imputed implants)		
Rasmusson (2005)	1992	PCS	36	64 (59, 82)	(23,13)	22.2	8 (5.7)	Straumann	University
Roccuzzo (2010)	1996	PCS	35	56 (32, 64)	(ND)	8.6	3 (1.2)	Friadent	SPP
Agamy (2010)	N/D	PCS	31	62 (53, 71)	(12,19)	0.0	0 (0)	Sweden & Martina	University
Covani (2012)	1996	PCS	91	49 (23, 75)	(36,55)	15.7	17 (4.2)	NobelBiocare (Brånemark)	University
Degidi (2012)	2000	PCS	59	50 (31,68)	(21,27)	26.2	17 (5.1)	NobelBiocare (Brånemark)	University
Ostman (2012)	2001	PCS	46	52 (N/D)	(18,28)	0.0	0 (0)	Biomet 3i	University
Vigolo (2012)	1998	RCT	18	33 (27, 42)	(8,10)	11.1	2 (1.1)	Biomet 3i	University
Calvo-Guirado (2014)	2002	PCS	64	39 (29, 60)	(32,32)	3.1	2 (0)	Straumann	University
Roccuzzo (2013)	1998	PCS	149	51 (30, 64)	(N/D)	17.4	26 (6.1)	Friadent	University
Meyle (2014)	2003	PCS	20	49 (39, 57)	(9,11)	0.0	0 (0)	Biomet 3i	University
Schropp (2013)	1999	RCT	63	46 (20, 74)	(28,35)	28.1	18 (1.6)	Biomet 3i	SPP
Vigolo (2015)	2002	RCT	44	51 (37,58)	(21,23)	11.4	5 (1.7)	Straumann	University
van Velzen (2014)	1997	PCS	250	50 (16,84)	(106,144)	29.2	73 (14.7)	NobelBiocare (Brånemark)	University
56Walton (2016)	2001	PCS	35	46 (15,79)	(17,18)	22.9	8 (1.1)	Sweden & Martina	SPP
Cassetta (2015)	2001	PCS	16	58 (48,69)	(12,4)	0.0	0 (0)	Dentsply (Astra)	University
Degidi (2016)	2001	PCS	114	53 (37,68)	(ND)	24.0	30 (12.4)	NobelBiocare: Southern	University
Ma (2015)	2005	RCT	40	64 (55,76)	(19,21)	40.0	16 (32.0)	Straumann	University
Zhang (2016)	2006	PCS	12	56 (40,73)	(4,8)	8.3	1 (0.7)	Dentsply (Astra)	University

Abbreviations: F – female; M – male; N/D - Not disclosed; PCS – Prospective Cohort Study; RCT – Randomized Controlled Trial; SPP – Specialist Private Practice.

of the funnel plot which was confirmed by Egger's test.

For the sensitivity meta-analysis of imputed missing data the overall summary estimate was significantly lower when compared to the complete case analysis, at 93.2% (95% CI: 90%–96%) $p < 0.05$, and the prediction interval was considerably wider at 77%–100%. There were no significant differences in any of the subgroup analyses except for overdentures within the superstructure subgroup, which now had dropped further to a survival rate of 59% (95% CI: 45%–73%). For meta-regression, age group was not a significant factor, but patient dropout was, reducing implant survival by 0.6% for every 1% of patient LTFU. Publication bias was reduced when the imputed data was added back in, and Eggers test confirmed symmetry in the funnel plot.

The sensitivity analysis produces some interesting results. The use of the RRR highlighted the differences in interpretation of benefits (survival) and harms (failure) The imputed data meta-analysis had a small non-significant reduction in the RRR for implant survival of 0.967 at 10-years but almost a doubling in the risk of implant failure (RRR = 1.8) which was significant ($p < 0.5$). There were similar results for age, overdentures, LTFU ≥ 20% and studies associated with a high risk of bias (RRR ranged from 2.13 to 2.99).

4.2. Strengths and limitations

4.2.1. Strengths

This systematic review was specifically designed to investigate whether there were any methodological weaknesses in the current systematic reviews on 10-year implant survival that may influence the summary estimate and its effect on real world clinical decision making. Explicit protocol driven study selection, data extraction and data synthesis methods to reduce potential risk of bias in the results were used. By undertaking a sensitivity meta-analysis including a prediction interval [34] it was possible to test the robustness of the main results and hypothesize on the effects of a more plausible model of increased implant failure in the patients who did not attend the 10-year review.

4.2.2. Limitations

The sensitivity analysis followed the imputation model proposed by Akl [33,34]. There was no direct data relating to an increase adverse event rate in LTFU data in the dental literature, however a paper was published on poor patient attendance patterns where the rate of tooth loss was approximately twice that of regular attenders, but they were not LTFU or implant patients [69]. The true REI correction factor would most likely lie between 2 and 5, but with published implant survival rates close to 100% Akl's recommendation was to examine the impact of the more extreme evidence-based assumption from Geng, this advice was followed [70].

The search may not have found all the prospective studies that fulfilled the inclusion criteria due to limitations in the key words used by the authors in some of these papers [31] during the electronic searches.

There was a lack of clarity in some studies as to what constituted failure, especially where the implant was fixed under a rigid framework and could only be removed by clinical intervention of the assessment team. A wider definition of failure (ICOI Pisa Health Scale for Dental Implants) was applied in the sensitivity meta-analysis to capture these additional implants [35]. Additionally research teams developing common definitions of oral health, could including patient specific input to help set a common baseline for future systematic reviews or guidelines as recommended in the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool for guideline assessment [71–73]

The included studies all suffered from selection bias making the results only representative of implants placed in university or specialist practice.

4.3. Areas for discussion

LTFU in any study can impact the validity of the outcome being measured especially if the study carries on over a long period of time [74–76]. This review identified significant differences between the two meta-analyses that were not apparent when the results are viewed separately, most notably age associated with the LTFU of > 20%. Regarding increasing age there were a number of points to consider; Chrcanovic reported a statistically significant reduction in the odds ratio of implant survival of 0.98 per year where implant failure clustered round certain individuals [77]. The 2017 Consensus report of the European Federation of Periodontists (EFP) concluded there was a

Table 4
Summary results for implant survival, age group and superstructure.

Study	Implants (complete cases)			Implants (imputation of missing data)				Subgroups				
	Total number of implants	Number remaining at 10-years	Estimates survival after 10 years (%)	Total number of implants	Number remaining at 10 years	Estimates survival after 10 years (%)	Imputed additional failed implants†	Age group‡	Superstructure type			
									SC	FPP	FAP	OD
Rasmusson (2005)	199	193	96.98	199	187	93.97	6	2			32	
Roccuzzo (2010)	77	74	96.10	77	73	94.81	1	1	ND	ND	ND	ND
Agamy (2010)	78	72	92.31	78	72	92.31	0	2		31		
Covani (2012)	159	146	91.82	171*	142	83.04	4	2	159			
Degidi (2012)	210	205	97.62	210	200	95.24	5	2		59		
Ostman (2012)	121	118	97.52	121	118	97.52	0	1	22	21	7	
Vigolo (2012)	36	34	94.44	36	33	91.67	1	1	36			
Calvo-Guirado (2014)	86	83	96.51	86	83	96.51	0	1	86			
Roccuzzo (2013)	252	246	97.62	252	240	95.24	6	1	ND	ND	ND	ND
Meyle (2014)	54	52	96.30	54	52	96.30	0	1	54			
Schropp (2013)	63	60	95.24	64*	58	90.63	2	2	63			
Vigolo (2015)	132	129	97.73	132	127	96.21	2	1		44		
van Velzen (2014)	506	496	98.02	506	481	95.06	15	2	113	339		54
Walton (2016)	35	34	97.14	35	33	94.29	1	2	35			
Cassetta (2015)	188	184	97.87	188	184	97.87	0	2			32	
Degidi (2016)	284	274	96.48	284	262	92.25	12	2	ND	ND	ND	ND
Ma (2015)	117	101	86.32	117	69	58.97	32	2				39
Zhang (2016)	91	89	97.80	91	88	96.70	1	2			12	
Totals	2688	2590	96.35	2701	2502	92.63	88	NA	568	494	83	93

* Increase in denominator to add implants that were excluded after initial inclusion.
† Imputation based on 5-fold increase in long term failure rate (1-survival rate) in the lost-to follow-up group deducted from the published number of implant remaining.
‡ Age (divided into two groups) 15-64 years = 1, Max age ≥65 year = 2.
Abbreviations: SC - Single crown; FPP - Fixed partial prosthesis; FAP - Full arch prosthesis; OD – Overdenture; N/D – Not disclosed.

general reduction in oral health as the population aged [78].The latest EFP consensus report on peri-implantitis suggest a non-linear accelerating of infection effecting 14–30% of implants [79] over time that ultimately may lead to the loss of the implant [80] and a systematic review by Sgolastra and co-workers concluded that patients with periodontitis had higher risk of peri-implantitis and implant loss [81].

As patients age there are increasing demands on their general health in the form of multimorbidity (two of more chronic morbidities such cancer and diabetes) that would originally have excluded them from the study and may have an effect on long-term implant survival [82].There was also a gradual reduction in the emotional impact of tooth loss, so as age increases there is less concerned with reporting or replacing a missing tooth [83].

This combination of progressive chronic implant infection, clustering of implant failure, general health problems, and reduced concern about replacing missing teeth or seeking dental care could justify a higher adverse event rate in the LTFU group.

4.4. Effect on publication bias

Asymmetry in the 'complete case' meta-analysis may be due to the implausible management of the LTFU data, as the symmetry improved once the missing data was corrected for in the sensitivity meta-analysis.

4.5. Prediction intervals

Clinical interpretation of meta-analysis results can be misleading as the result comprises of the summary effect size combined with a confidence interval and p value. This may be complicated further with interpretation of the heterogeneity in the form of I^2. The summary estimate is the mean value of multiple mean values, and the variability between the individual studies, for this systematic review this varied between moderate for the primary outcome and high for the secondary outcome. Importantly the prediction interval estimates where the true effects are to be expected for 95% of similar studies that might be conducted in the future [45], and this may alter the clinical decision-making process. Current systematic reviews have potentially overestimated survival and underestimate implant loss as there were no significant difference in implant loss between younger and older patients [8,84]. The prediction interval allows the clinician to create a more accurate patient specific prognosis for future implant success than the usual summary estimate. In plain language, for a young patient who has lost a tooth as the consequence of trauma, the risk of failure could be predicted as low as 1-in-100 and for an elderly patient whose tooth

Table 5
Consensus risk of bias judgements by study and domain (Hoy).

	Target population a close representation of national population.	Sampling frame a true or close representation of the target population	Was random selection or census undertaken to select the sample?	Was non-response bias minimal?	Data collected directly from subjects.	Acceptable case definition	Measurement shown to have reliability.	Same mode of data collection for all subjects.	Length of shortest prevalence period appropriate	Was numerator(s) and denominator(s) appropriate	Risk of Bias
Walton (2016)	✗	✗	✓	✗	✓	✓	✓	✓	✓	✓	**M**
Degidi (2016)	✗	✗	✗	✗	✓	✓	✓	✓	✓	✗	**H**
Ma (2016)	✗	✗	✓	✗	✓	✓	✗	✓	✓	✗	**H**
Zhang (2016	✗	✗	✓	✓	✓	✓	✓	✓	✓	✓	**M**
Vigolo (2015)	✗	✗	✗	✓	✓	✓	✓	✓	✓	✓	**M**
Cassetta (2015)	✗	✗	✗	✓	✓	✓	✗	✓	✓	✗	**H**
van Velzen (2015)	✗	✗	✓	✗	✓	✓	✗	✓	✓	✗	**H**
Calvo-Guirado (2014)	✗	✗	✓	✓	✓	✓	✓	✓	✓	✓	**M**
Meyle (2014)	✗	✗	✗	✓	✓	✓	✗	✓	✓	✓	**M**
Roccuzzo(2014)	✗	✗	✓	✗	✓	✓	✓	✓	✓	✓	**M**
Schropp (2013)	✗	✗	✓	✗	✓	✓	✓	✓	✓	✗	**M**
Covani (2012)	✗	✗	✗	✗	✓	✓	✓	✓	✓	✗	**H**
Degidi (2012)	✗	✗	✗	✗	✓	✓	✓	✓	✓	✗	**M**
Ostman (2012)	✗	✗	✓	✓	✓	✓	✗	✓	✓	✓	**M**
Vigolo (2012)	✗	✗	✓	✓	✓	✓	✓	✓	✓	✓	**M**
Roccuzzo (2010)	✗	✗	✓	✓	✓	✓	✓	✓	✓	✓	**M**
Agamy (2010)	✗	✗	✓	✓	✓	✓	✓	✓	✓	✓	**M**
Rasmusson (2005)	✗	✗	✓	✗	✓	✓	✓	✓	✓	✓	**M**

Risk of bias: **L** – Low; **M** - Moderate; **H** - High.

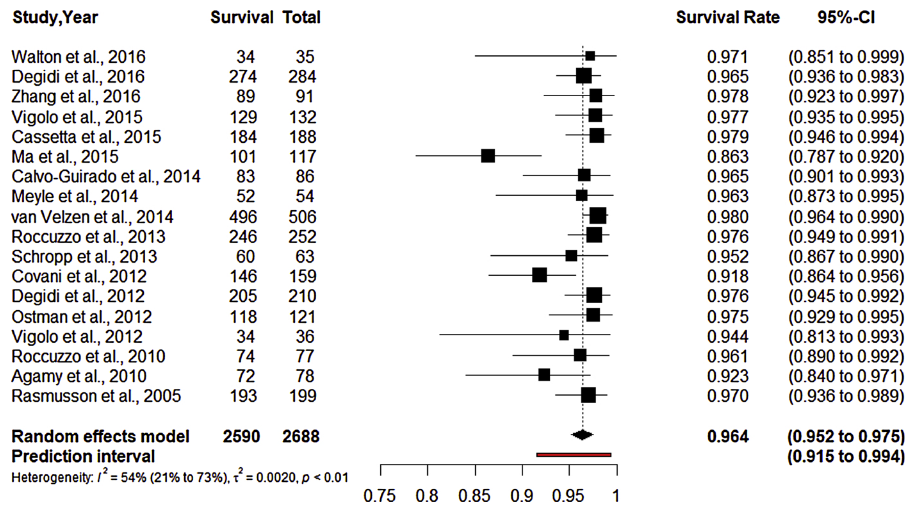


Fig. 2. Forest plot displaying the results of a meta-analysis of 10-year implant survival using complete case data.

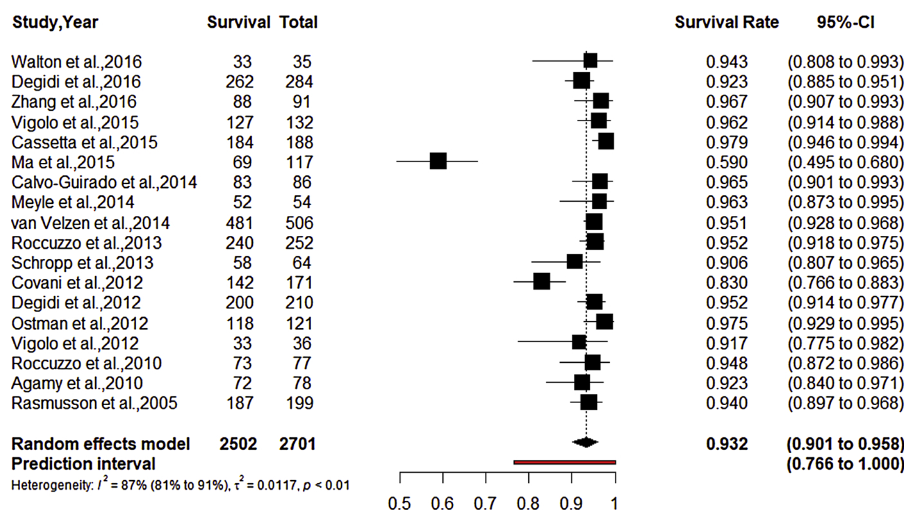
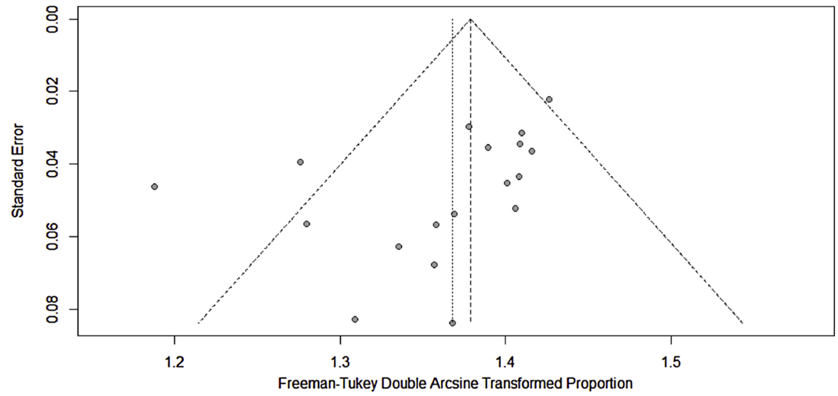


Fig. 3. Forest plot displaying the results of a sensitivity meta-analysis of 10-year implant survival using imputed data.

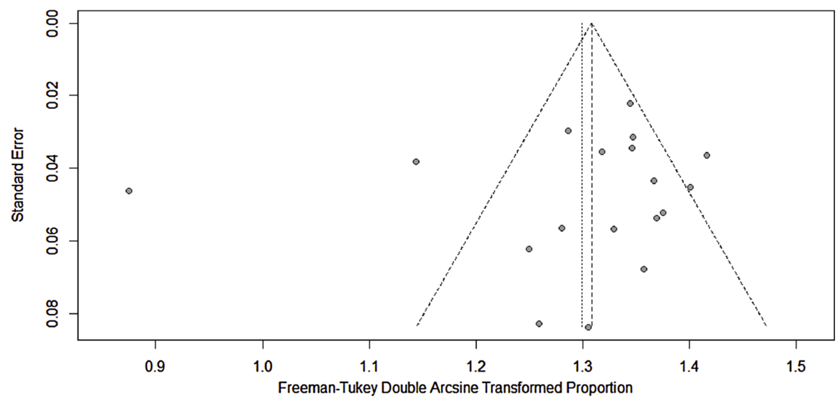
Table 6
Sensitivity analysis comparing complete case LTFU vs. imputed data LTFU.

Subgroups	Imputed data group		*P-value**	Relative Risk Ratio of:		Absolute difference between CDG and IDG	*P-value*† p < 0.05 in bold
	Survival rate	95% CI		Survival rates	Failure rates		
Overall results	0.932	(0.901 to 0.958)	–	0.967	1.888	0.032	0.044
Age							
Max Age ≥65	0.915	(0.871 to 0.951)	0.157	0.953	2.130	0.045	0.038
Max Age < 65	0.958	(0.912 to 0.989)		0.987	1.444	0.013	0.552
Superstructure							
Single crown	0.919	(0.877 to 0.954)	< 0.001	0.970	1.544	0.028	0.215
Fixed partial prosthesis	0.949	(0.906 to 0.980)		0.979	1.669	0.020	0.331
Full arch prosthesis	0.963	(0.926 to 0.988)		0.987	1.504	0.012	0.482
Overdenture	0.590	(0.445 to 0.727)		0.683	2.999	0.274	0.001
Lost to follow-up							
≤ 19% LTFU	0.949	(0.911 to 0.978)	0.150	0.983	1.457	0.016	0.398
≥ 20% LTFU	0.903	(0.843 to 0.951)		0.980	2.622	0.060	0.040
Sensitivity							
Moderate risk of bias	0.950	(0.916 to 0.977)	0.061	0.980	1.613	0.019	0.270
High risk of bias	0.884	(0.812 to 0.940)		0.927	2.522	0.070	0.043
Excl. only Ma et al., 2015	0.946	(0.929 to 0.960)		0.974	1.862	0.025	0.005

Abbreviations: CDG-Complete data group; IDG – Imputed data group; CI – Confidence interval.
* P-value obtained from a paired test of the difference in proportions (between subgroups).
†P-value obtained from a paired test of the difference in proportions (between scenarios).



A. Funnel plot of 'complete case' meta-analysis



B. Funnel plot of 'imputed data' meta-analysis

Fig. 4. Funnel plots comparing complete case and imputed meta-analysis.

Table 7
Summary of evidence quality across studies (GRADE).

Levels of quality of a body of evidence in the GRADE approach			
Criteria for assessing quality of evidence of outcome	Results section	Comments	Quality of evidence
Risk of bias	Selection bias and loss-to-follow up	All 18 studies were prospective with only 4 defined as randomised trials. The randomisation did not relate to implant selection which was universal to all the studies. Loss to follow up ranged from 0% to 40% after 10-years.	⨁○○○ Very low
Inconsistency	Heterogeneity	Heterogeneity was moderate with a wide confidence interval I^2 = 54 (85% CI:21-72) due to variability in patient selection and intervention in the studies even though surgical protocol for the implant placement itself was generally consistent across the studies.	⨁⨁○○ Low
Indirectness	Sample not representative of national or target population	All the studies were carried out in a university teaching hospital or specialist private practice. Considering the global distribution of dental implants 8 out of the 18 studies were undertaken in one European country.	⨁○○○ Very low
Imprecision	Missing data analysis	The optimal information size was sufficient to support the precision of the effect size (Guyatt et al., 2011).However the high number of patients lost-to-follow up were considered as ignorable data	⨁⨁○○ Low
Publication bias	Symmetry in funnel plot	The funnel plot and Egger test suggest symmetry in the funnel plot however there are 2 outliers present.	⨁○○○ Very low

Overall judgement and conclusion: ⨁○○○ Very low. Even though the studies were all prospective with moderate heterogeneity they were highly vulnerable to selection bias and missing data.

loss is due to severe restorative failure and periodontal bone loss the risk could be as high as 1-in-5 over a 10-years period.

5. Conclusion

Previous analytic approaches potentially overestimate implant survival. This more realistic loss to follow-up analysis suggests a potential doubling in the risk of implant loss in the older age groups who may have the highest demand for implants. The use of prediction intervals can help the clinician provide more accurate patient specific prognosis than the usual summary estimate. This review demonstrates the positive and negative effects of missing data analysis. Researchers need to develop reasonable evidence-based assumptions regarding the handling of missing data. Finally, prediction intervals need to become a routine component in meta-analysis results to assist in their interpretation.

Conflict of interest and sources of funding statement

"The authors declare that there are no conflicts of interest in this study".

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