Why we should be looking for ear lobe creases. A systematic review and meta-analysis of diagonal ear lobe crease and coronary artery disease.

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Abstract

Objectives The association between diagonal ear lobe crease (DELC) and cardiovascular disease was first suggested in 1973 although some studies have attributed this to confounding cardiovascular factors. This review looked to see if there is a significant association between DELC and angiography-confirmed coronary artery disease (CAD) independent of other risk factors. Design Systematic review and meta-analysis of selected studies using the PRISMA checklist. Setting 12 different hospitals with angiography in eight countries. Participants 4960 adult patients undergoing coronary angiography. Main Outcome Measures * Presence/absence of diagonal ear lobe crease * Diagnostic Odds Ratio * Sensitivity/Specificity Results 12 studies were included in the meta-analysis. Findings from our study suggest: * Patients with DELC have a 4x increased likelihood of having CAD (OR 4.61 P<0.00001). * The relationship between DELC and CAD was independent of age and all other conventional cardiovascular risk factors. * Bilateral DELC has a stronger association with CAD than unilateral DELC. * Presence of DELC has insufficient sensitivity / specificity to be used as a diagnostic test for cardiovascular disease but instead should be used as a risk marker. Conclusions We found that DELC is associated with CAD independently of other known cardiovascular risk factors including age. Histology studies indicate that atherosclerosis is causing DELC and patients with DELC appear to have an increased risk of CAD. It has insufficient sensitivity or specificity to be used as a diagnostic test but should be used as a valuable risk marker to be aware of whilst examining ears.

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Abstract

Objectives

The association between diagonal ear lobe crease (DELC) and cardiovascular disease was first suggested in 1973 although some studies have attributed this to confounding cardiovascular factors. This review looked to see if there is a significant association between the presence of a DELC and angiography-confirmed coronary artery disease (CAD) independent of other risk factors.

Design

Systematic review and meta-analysis of selected studies using the PRISMA checklist.

Setting

12 different hospitals with angiography in eight different countries

Participants

4960 adult patients undergoing coronary angiography.

Main Outcome Measures

- Presence / absence of diagonal ear lobe crease
- Diagnostic Odds Ratio
- Sensitivity / Specificity

Results

12 studies were included in the meta-analysis. Findings from our study suggest:

- Patients with DELC have a 4x increased likelihood of having CAD (OR 4.61 P<0.00001).
- The relationship between DELC and CAD was independent of age and all other conventional cardiovascular risk factors.
- Bilateral DELC has a stronger association with CAD than unilateral DELC.
- Presence of DELC has insufficient sensitivity / specificity to be used as a diagnostic test for cardiovascular disease but instead should be used as a risk marker.

Conclusions

We found that DELC is associated with CAD independently of other known cardiovascular risk factors including age. Histology studies indicate that atherosclerosis is causing DELC and patients with DELC appear to have an increased risk of CAD. It has insufficient sensitivity or specificity to be used as a diagnostic test but should be used as a valuable risk marker to be aware of whilst examining ears.

5 Key Points

- The relationship between a diagonal ear lobe crease (DELC) and cardiovascular disease has been known about for over 45 years but some have suggested it is a result of a confounding factor and there have been no studies in otolaryngology publications.
- We performed a PRISMA based systematic review and meta-analysis involving 12 studies and 4960 patients.
- Findings from our study suggest:
- Patients with DELC have a 4x increased likelihood of having Coronary Artery Disease (CAD) (OR 4.61 P<0.00001).
- The relationship between DELC and CAD is independent of age and all other conventional cardiovascular risk factors and that bilateral DELC has a stronger association with CAD than unilateral DELC.
- Presence of DELC has insufficient sensitivity / specificity to be used as a diagnostic test for cardiovascular disease but instead should be used as a risk marker.

Key words: Ear lobe crease, earlobe, Frank's sign, coronary disease

Figures

Introduction

An association between a diagonal ear lobe crease (DELC) and cardiovascular disease was first suggested by Sanders T. Frank in 1973 in the New England Journal of Medicine[(1)]. Since then there have been numerous

further studies that have investigated the association of 'Frank's Sign' with carotid disease, cerebral vascular disease and diabetic retinopathy. Whilst almost all of the studies since then have found a correlation between DELC and cardiovascular disease, there is disagreement on whether this is an independent association or whether both of these are related to increasing age or other potential confounding cardiovascular risk factors [(2)].

The purpose of this meta-analysis is therefore to determine if there is a significant association between the presence of a diagonal ear lobe crease (Fig. 1) and coronary artery disease (CAD) independent of other risk factors. Although there have been other reviews that have looked into this [(3)], these have included autopsy studies or clinically diagnosed CAD and none have specifically looked at studies solely using coronary angiography which is the gold standard for confirming CAD[(4-6)]. At the same time, although this is an aural sign, there have been no studies in any otology journals and no reports in any otolaryngology literature. We believe this is the first literature review and meta-analysis that solely looks at patients with DELC undergoing angiography and the first article about this topic in an otology publication.

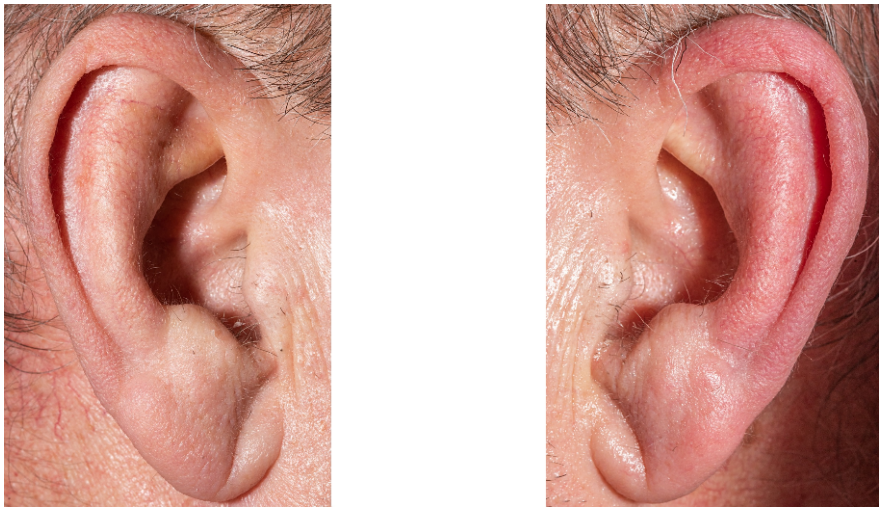

Figure 1: Examples of diagonal ear lobe creases

Methodology

Protocol and Information Sources

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist[(7)] was used to report this review. The PUBMED database was searched on August 12th 2020 using the following separate terms: ear lobe crease(s), earlobe crease(s), Frank's sign.

Study selection, data collection and bias

Retrieved studies were filtered on title and abstract and where there was any doubt, the study was accepted to the next level. Only original studies equal to or above OCEBM Level 4 evidence[(8)]that reported on the presence of a diagonal ear lobe crease in patients undergoing coronary angiography were included. Selected studies were then assessed independently by both authors for quality and bias using CASP checklists[(9)]. Differences were resolved by discussion. Objective data were extracted from the studies and summarized into tables and meta-analysis was performed using Revman 5.4[(10)].

Results

3.1 – Study selection

The search retrieved 355 individual studies that were filtered by language, title and abstract leaving 21 original studies. Nine studies were then excluded at full text, mostly for not reporting on patients who had undergone coronary angiography although one study was excluded for unclear results[2] and another excluded for reporting on the same patients as another study[11]. This left 12 original studies published between 1974 and 2017 included in this review. Figure 2 shows the selection process.

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Figure 2: Flow diagram of study selection process

3.2 – Study Characteristics

Key characteristics of the 12 studies are included in Table 1 and assessed quality of studies is shown in Appendix 1. All the studies were case-control studies and cumulatively included 4960 patients (min 125 max 1424) across eight countries and it is unlikely that this involved any duplicated patients due to the geographical and chronological spread of the studies. For each study the case population was well described as patients undergoing coronary angiography. Most studies reported relatively consistent definitions of DELC. This was typically a deep crease extending obliquely from the tragus towards the outer border of the ear lobe although the distance varied from a third to complete. All studies defined the presence of coronary artery disease as >50% stenosis of at least one major epicardial vessel, except for three studies which used a threshold of >70% stenosis[6, 12, 13].

3.3 Risk of bias within studies

Bias was mostly excluded from studies by the presence of DELC being measured without knowing the cardiac history shortly before undergoing angiography and with fairly consistent definitions of DELC and CAD. No patients were lost to attrition however two studies[4, 6] used non-cardiac patients as controls and it was assumed they had no CAD without undergoing angiography. Other potential biases are mentioned further in results.

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Table 1: Key characteristics of included studies

3.4 Overall results of studies

All 12 studies were included in the pooled analysis. This included 2415 cases and 2545 controls. The pooled results (Figure 3) suggest that patients with DELC have an increased likelihood of having coronary artery disease. (OR= 4.61, 95% CI: 3.17 to 9.60). There was significant heterogeneity among studies (I^2=83%, P<0.00001) whilst test for overall effect, Z, was 8.01 (p<0.00001). Ten of the 12 studies found a significant association between DELC and CAD. The two studies that found no significance association [14, 15] were poorer quality studies which both attributed their findings to age without any statistical analysis.

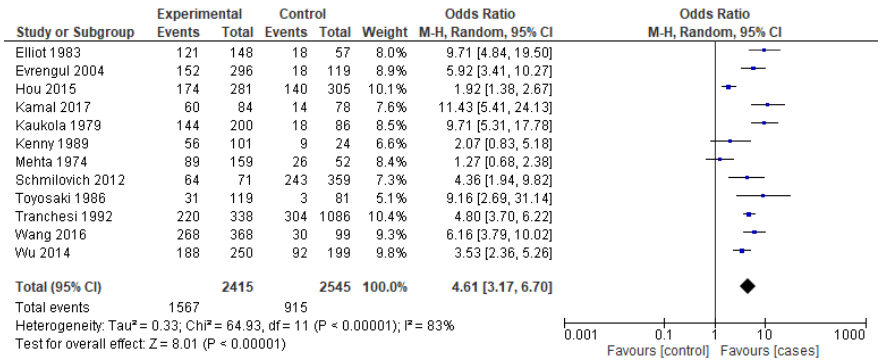

Figure 3: Forest Plot of Diagnostic Odds Ratios

3.4.1 – Sensitivity and Specificity

Sensitivity of DELC as a diagnostic test for CAD ranged from 0.26 to 0.90 and specificity ranged from 0.32 to 0.96 (Figure 4). This variance, as demonstrated on the ROC curve (Figure 5), suggests that DELC by itself is not suitable as a diagnostic test for CAD.

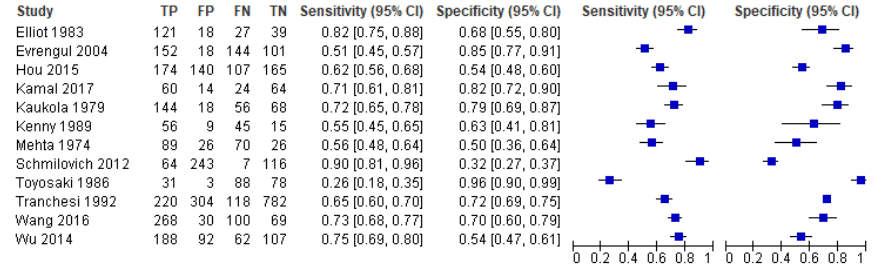

Figure 4: Sensitivity and Specificity of Studies

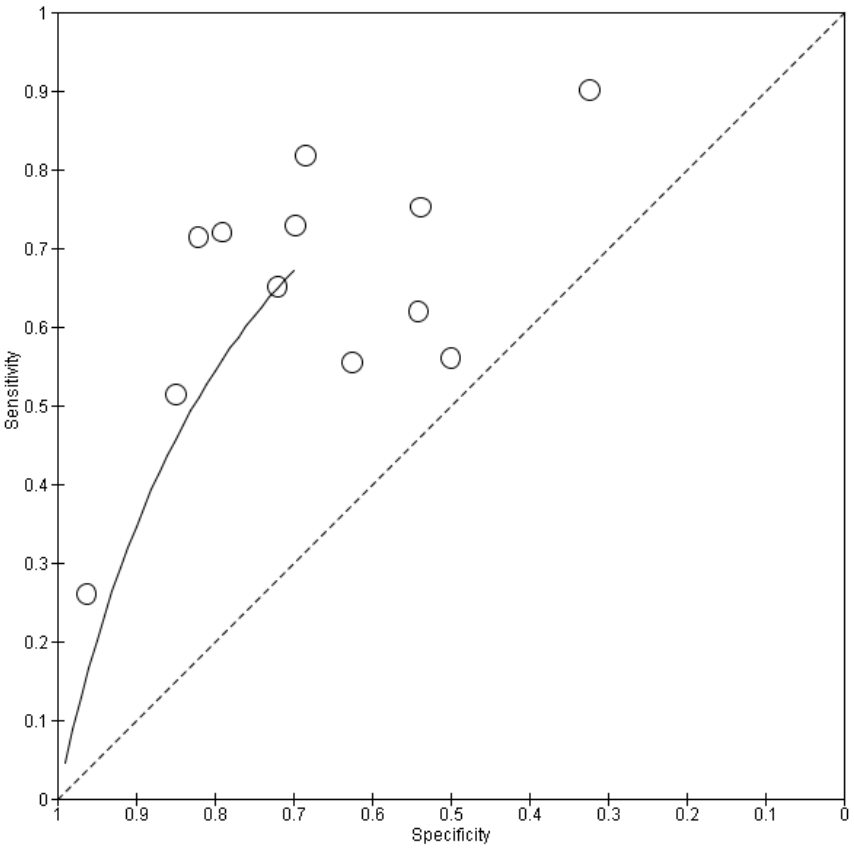

Figure 5: Receiver Operating Characteristic (ROC) Curve

3.4.2 - Bilateral vs Unilateral DELC

Three studies investigated unilateral and bilateral DELC separately[4, 16, 17], two studies just looked at bilateral DELC[11, 13], two studies included both unilateral and bilateral DELC combined [6, 18] and in five studies it was not clear which was used. Whilst this raises concerns, it is noted that in the three studies which compared bilateral and unilateral DELC, unilateral DELC was found to have either a reduced association with CAD[17] or no significant association[4, 16]. The breakdown is shown in Table 2. It is therefore believed that in any studies that included unilateral DELC with bilateral DELC, this would have had a diluting effect in the odds ratio and association with CAD.

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Table 2: Breakdown of diagnostic odds ratio (DOR) for unilateral vs bilateral DELC

3.4.3 Age

In studies which reported a mean age there was good comparison between case and control groups (Table 1). Ten of the studies looked at the association with age either by looking at different age cohorts or by performing multivariate regression analysis. Of these ten, four studies looking at cohorts found a significant association between DELC and CAD in all age brackets investigated[5, 6, 12, 18] whilst four[11, 13, 16, 17] using

multivariate regression analysis found that DELC was independently and significantly associated with CAD when compared with age. Only two studies[14, 15] suggested that DELC was directly due to age and they provided no statistical analysis to support their view. Of the four studies which looked at different age cohorts, only one[6] provided enough detail to look at the diagnostic odds ratio for different 10 year age cohorts. There was no obvious pattern with the ratios although the DOR was greatest in the youngest cohort (<40yo) and smallest in the oldest cohort (>70yo).

3.4.4 – Gender

It was noted that most studies which recorded gender had a disparate gender ratio between the case and control groups (Table 1). This is partly explained as female patients have a lower prevalence of coronary artery disease and are therefore more likely to be in the control group however only Kamal *et al* gender matched each group[4]. Although there was a reported increased prevalence of DELC and CAD in male patients in most studies, only one study [17] looked at the odds ratio for both genders independently and found that women had a greater association between DELC and CAD (Female OR 6.368 95% CI 2.961 to 13.694 vs Male OR 5.420 95% CI 2.804 to 10.477). No other studies reported results in sufficient detail to allow comparison with this study.

3.4.5 - Ethnicity

Only two studies looked at different ethnic populations separately within their study. One[6] found that DELC was more prevalent in caucasian than non-caucasian populations but there was still a significant association with CAD in both groups. Another[12] attempted to investigate this as well but cases and controls were not well matched on gender and race and no meaningful results were obtainable. Overall the twelve studies covered multiple ethnic populations from around the globe and it is believed that this suggests the findings are applicable to a wider population although variations between ethnic groups can not be excluded.

3.4.6 – Other cardiovascular risk factors

Eight of the studies[5, 11, 13, 14, 16-19] used multivariate regression analysis to look at the relationship between DELC and other conventional cardiovascular risk factors including hypertension, hyperlipidaemia, smoking status, diabetes mellitus, obesity and family history. Although four studies [11, 13, 17, 18], found a significant correlation between DELC and certain risk factors such as age, male gender, hypertension and smoking status this did not correspond with the presence of CAD. Instead all eight studies found that DELC was independently and significantly associated with CAD when compared against all conventional risk factors.

3.4.7 – Severity of disease

Four studies looked at the association between DELC and severity of CAD as assessed by the number of stenosed coronary arteries. Of these, two[16, 18] found no significant association between the number of diseased vessels and DELC but two[5, 6]found that multi-vessel disease was more common in patients with DELC.

3.5 Publication Bias

No publication bias across studies was found especially as two of the included studies[14, 15] suggested that there was no association between DELC and CAD.

Discussion

Summary of evidence

This study investigated if there is a significant association between the presence of a diagonal ear lobe crease (DELC) and coronary artery disease (CAD) independent of age. By using the gold standard diagnosis for CAD, angiography, we were able to provide a more objective analysis than other reviews which have included autopsy studies and clinically diagnosed heart disease[3]. Our study found that patients with DELC have an increased likelihood of having CAD. Also despite some previous studies suggesting that DELC was simply a

result of age, all ten of the included studies that looked at this found that the relationship between DELC and CAD was independent of age and all other conventional cardiovascular risk factors.

We also looked to see if the diagnostic odds ratio varied between different cohorts. In looking at different age groups, only one study[6] provided their findings for each age bracket and although it found that the diagnostic odds ratio was greatest in the youngest cohort, the population size of each cohort was relatively small and it is difficult to assess the validity of this finding without other studies. Similarly, only one study looked at different odds ratio between genders and found that it was greater in women than men (OR 6.368 vs 5.420) however it is difficult to assess this effect overall in our analysis as there was frequently a disparate gender ratio between the case and control groups. Whilst this is due to poor recruitment, it may partly be influenced by there being a reduced prevalence of CAD in women and also some studies excluding patients with ear lobe piercings causing an iatrogenic DELC. Other studies[20] have found no difference in the prevalence of DELC between males and females.

As the included studies spanned eight different countries it is believed that the results are applicable to multiple ethnic populations. However it is difficult to determine the impact of ethnicity especially as there are few studies which look at the general prevalence of DELC in a healthy population. Without knowing the generalised prevalence of DELC and relationship with CAD in different populations it is difficult to ascertain the impact of ethnicity.

Although this study found that patients with DELC have an increased likelihood of having CAD, there was wide variance in the sensitivity and specificity of DELC as a diagnostic test. This supports findings from other studies that indicate DELC should only be used as a physical marker not a diagnostic clinical test for CAD[12].

Pathophysiology

At first there may not be any obvious link between coronary arteries and ear lobes however a few papers shed some light on this issue. Autopsy studies involving biopsies of ear lobes in patients with DELC found thickening of arterial walls and tears in the elastin[21] and that both earlobe and myocardium are supplied by end arteries without collateral circulation[22]. More recently Stoyanov[23] found that patients with DELC had diffuse fibrosis of an arterial vessel located at the base of the ear lobe crease and that this was associated with corresponding changes to myocardial tissue. As with our study, Stoyanov *et al* also found that this correlation was independent of age. As has been suggested in an earlier study[21], a reduced blood supply to the ear lobe could cause destruction of the elastin which manifests as creases in the ear lobe. It is feasible therefore that the same atherosclerotic processes that causes narrowing of coronary arteries may be causing a similar effect in the blood vessels supplying the ear lobe.

Limitations

There are three main limitations to this review. Firstly to include sufficient studies we could not restrict the time period and the selected studies ranged over forty years. However the methodology for identifying DELC and CAD remained unchanged in that period and we believe all included studies are relevant. Secondly, although studies used fairly consistent definitions of DELC and CAD, there was some variance especially in the length of the crease. Three studies also used >70% stenosis of at least one major epicardial vessel to define CAD when the majority used 50% but it is not possible to determine the impact that had on their results. Studies also varied in using unilateral or bilateral creases to define DELC, although it was noted that including unilateral creases appeared to reduce the odds ratio and therefore significant results were still considered valid. Lastly some studies used non-cardiac patients as controls and it was assumed that they had no coronary artery disease without undergoing angiography. We recommend that, for consistency, further studies assess bilateral DELC and use Shresta's[24] definition of a deep (>1mm) diagonal crease extending obliquely at least two-thirds from the tragus towards the outer border of the ear. This should be assessed by two examiners with the patient upright and patients with ear piercings which could cause iatrogenic creases should be excluded. Similarly CAD should be defined as >50% stenosis of at least one major epicardial vessel on angiography for both case and control groups.

Conclusion

This review looked to see if there is a significant association between the presence of a diagonal ear lobe crease (DELC) and coronary artery disease (CAD). We found that DELC is associated with CAD independently of other known cardiovascular risk factors including age and that patients with DELC appear to have an increased risk of CAD (OR 4.61) and this may be higher for patients with bilateral DELC. The variety of groups included in the selected studies suggest that this finding is relevant to the wider population. The sign does not have sufficient specificity or sensitivity to be used as a diagnostic test but instead it should be considered as a risk marker. For this reason we believe it is an important quick sign for clinicians to be aware of particularly those who more frequently examine ears. Histology studies have also indicated a feasible mechanism for atherosclerosis to cause DELC and explain this finding.

Funding and Conflicts of Interest

No funding was received for this review. The authors have no conflicts of interest to disclose.

Data sharing

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Appendix 1: Assessed Quality of Studies using CASP checklist[25]

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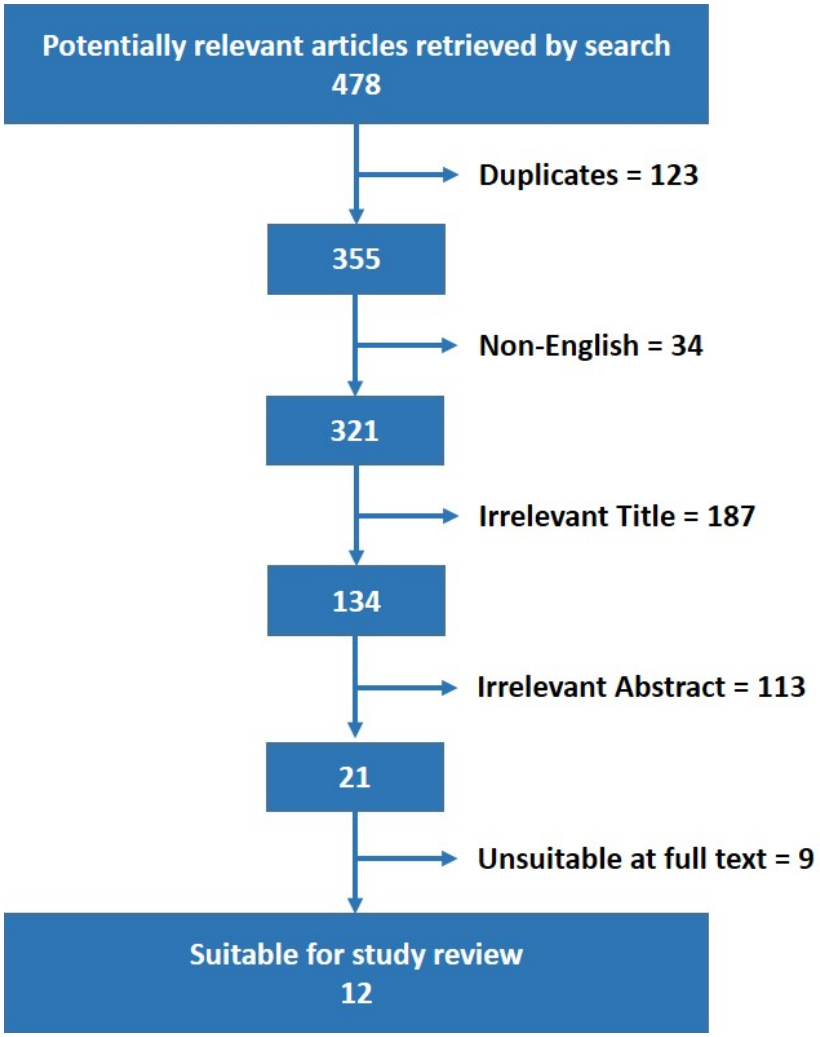

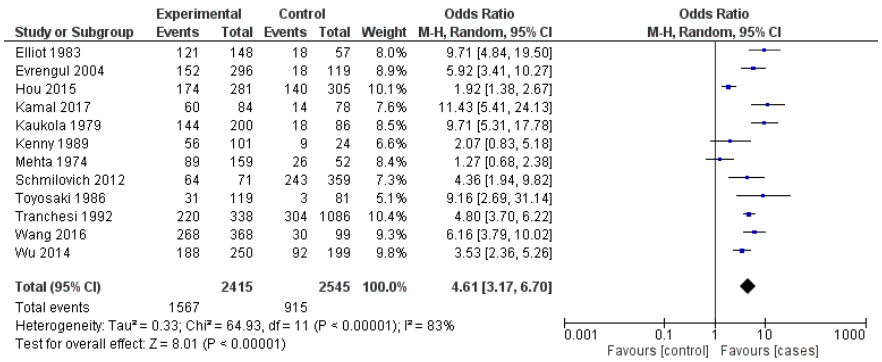

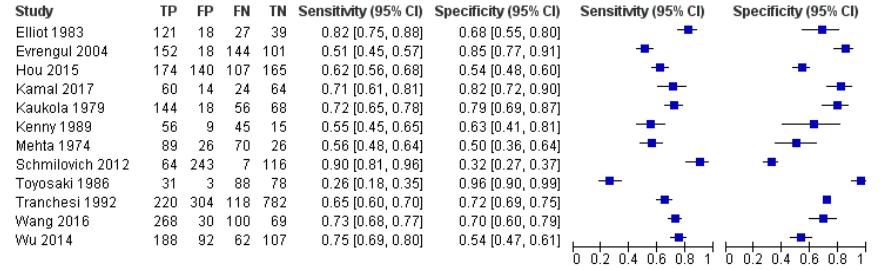

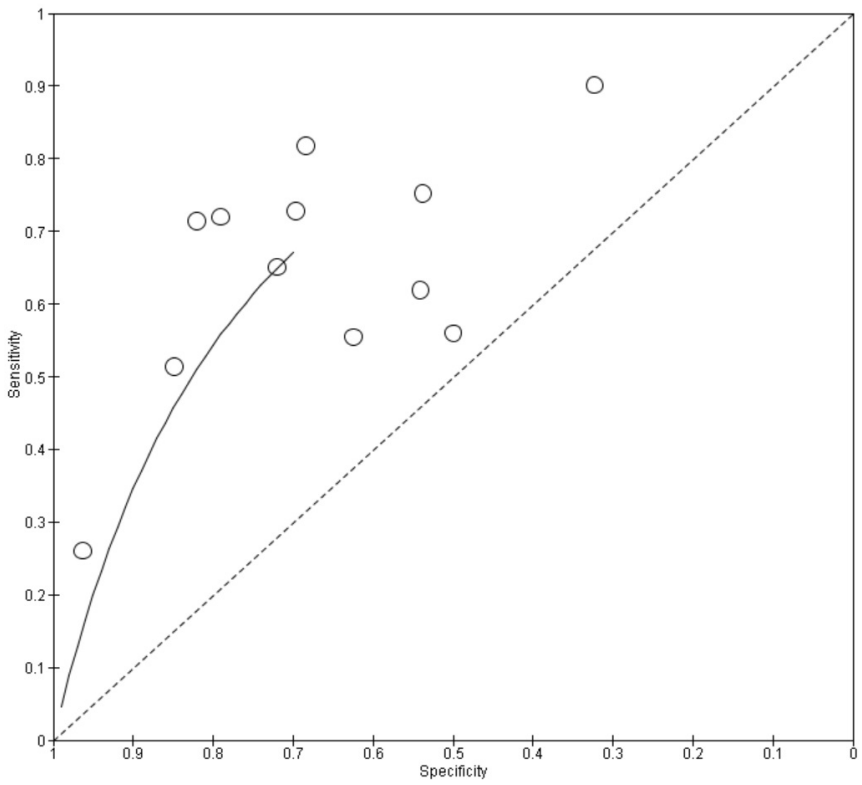

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Table 2 - Unilateral vs bilateral DELC.xlsx available at https://authorea.com/users/379460/articles/495661-why-we-should-be-looking-for-ear-lobe-creases-a-systematic-review-and-meta-analysis-of-diagonal-ear-lobe-crease-and-coronary-artery-disease