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# BMJ Open

## Overdiagnosis across medical disciplines: a systematic review

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3 1 **Title**  
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3 12 **Coverletter**  
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15 20  
16 21 Dear Sir/Madam,  
17

18 22 On behalf of my co-authors, I am writing you to submit our manuscript entitled, "*Overdiagnosis across medical*  
19 23 *disciplines: a systematic review*" for consideration for publication as a research article in the *BMJ Open*.  
20

21 24 The subject of overdiagnosis has become increasingly more popular over the last decades. There is significant debate  
22 25 in medical literature about its definition, impact and possible solution. Much progress has been made regarding the  
23 26 understanding of overdiagnosis in across medical disciplines, however a systematic analysis of current literature is still  
24 27 lacking. With this review we aim to fill this gap, showing that the term is being used for a wide range of papers, with  
25 28 varying scopes. This systematic review serves as a basis for researchers and clinicians in giving them insight in what  
26 29 has current focus in the scientific community, and where opportunities for further research lie.  
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28

29 30 We think that the readership of the BMJ Open is the most appropriate audience to which we would like to advocate  
30 31 our message. This paper is highly relevant for a broad audience, ranging from physicians reading diagnostic studies  
31 32 dealing with overdiagnosis, to clinical researchers seeking to explore whether overdiagnosis is being addressed in  
32 33 their field of research, to epidemiologists with a specific focus on methodological opportunities for further research.  
33

34 34 This paper has not been previously published and is not under consideration in any other peer-reviewed journal. All  
35 35 authors listed have contributed sufficiently to the project to be included as authors. To the best of our knowledge, no  
36 36 conflict of interest exists for any of the authors.  
37

38  
39 37 Thank you for considering our manuscript for review. We appreciate your time and are eagerly awaiting your  
40 38 response.  
41

42 39 With kind regards,  
43 40 Also on behalf of all other authors,  
44

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3 **Abstract**  
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6 **Objective** To provide insight into how and in what clinical fields overdiagnosis is studied, and  
7 give directions for further applied and methodological research.  
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9  
10 **Design** Systematic review

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12 **Data sources** Medline up to March 2016

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14 **Study selection** All English studies on humans, in which overdiagnosis was discussed as a  
15 dominant theme.  
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18 **Data extraction** Studies were assessed on clinical field, study aim (i.e. methodological or non-  
19 methodological), article type (e.g. primary study, review), the type and role of diagnostic test(s)  
20 studied, and the context in which these studies discussed overdiagnosis.  
21  
22

23 **Results** From 3802 studies, 1457 were included for analysis. Over half of all studies on  
24 overdiagnosis were performed in the field of oncology (51%). Other prevalent clinical fields  
25 included mental disorders, infectious diseases and cardiovascular disorders accounting for 10%,  
26 9% and 6% of studies respectively. Overdiagnosis was addressed from a methodological  
27 perspective in 27% of studies. Primary studies were the most common article type (61%). The  
28 type of diagnostic tests most commonly studied were imaging tests (32%), although these were  
29 predominantly seen in oncology and cardiovascular disease (84%). Diagnostic tests were studied  
30 in a screening setting in 42% of all studies, but as high as 74% of all oncological studies. The  
31 context in which studies addressed overdiagnosis related most frequently to its estimation,  
32 accounting for 57%. Methodology on overdiagnosis estimation and definition provided a source  
33 for extensive discussion. Other contexts of discussion included definition of disease,  
34 overdiagnosis communication, trends in increasing disease prevalence, drivers and  
35 consequences of overdiagnosis, incidental findings and genomics.  
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42 **Conclusions** Overdiagnosis is discussed across virtually all clinical fields and in different  
43 contexts. The variability in characteristics between studies and lack of consensus on  
44 overdiagnosis definition indicate the need for a uniform typology to improve coherence and  
45 comparability of studies on overdiagnosis.  
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4 80 **Strengths and limitations of this study**  
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- 6 81 - First complete overview of overdiagnosis across medical disciplines  
7 82 - Identification of the dominant clinical fields in which overdiagnosis is being studied, what  
8 83 characteristics these papers have, and in what context it is being studied  
9  
10 84 - Not a fully comprehensive systematic review, due to widespread variation in terminology  
11 85 and concepts used related to overdiagnosis  
12  
13 86 - Studies on incidental findings were likely missed due to usage of different terminology  
14 87 to describe overdiagnosis  
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## 89 Introduction

90 Overmedicalisation is the broad overarching term describing the use of “too much medicine”. (1)  
91 It encompasses various concepts such as disease mongering, misdiagnosis, overutilization,  
92 overdiagnosis and overtreatment. Initiatives relating to these concepts have begun to flourish  
93 on a global scale under the ‘Choosing Wisely’ initiative and in national programs such as Slow  
94 Medicine (Italy, the Netherlands and Brazil), Quaternary Prevention (Belgium) and Do not do  
95 (UK). (2, 3) A subcategory of the aforementioned concepts is overdiagnosis. This has become an  
96 even more popular term especially over the last two decades. (4-9) Furthermore, an annual  
97 conference going by the name of “Preventing Overdiagnosis”, dedicated to issues surrounding  
98 this concept, has been gaining popularity ever since its start in 2013, demonstrating a growing  
99 interest in the topic. (10) In this systematic review we will focus specifically on overdiagnosis.

100 Defining overdiagnosis is challenging and diverse definitions exist. (11, 12) In a narrow sense,  
101 overdiagnosis describes individuals receiving a diagnosis with a condition that would never have  
102 become symptomatic before the end of the individual’s life. (5, 7) However, overdiagnosis has  
103 also been described as giving a diagnosis that would not yield a net benefit. (1) These  
104 definitions are not similar, and thus may lead to different interpretations of (the extent of)  
105 overdiagnosis. Consequently, the mechanisms leading to overdiagnosis may also differ. Labeling  
106 an individual with a blood pressure over a certain threshold as hypertensive, and thus  
107 “diseased”, is conceptually different than not knowing whether one should diagnose an  
108 individual with a very small potentially malignant growth as having cancer, and thus “diseased”.  
109 Providing definitions in combination with mechanisms of overdiagnosis for a typology is  
110 challenging and source of extensive discussion. (13-17)

111 The range of overdiagnosis drivers is also extensive. It, amongst others, includes technological  
112 developments that detect smaller abnormalities than ever before which might not become  
113 clinically manifest. Furthermore, the use of large scale screening programs, inappropriate  
114 application of diagnostic criteria, legal incentives, cultural beliefs (i.e. that we should do  
115 everything in our power to find and treat disease) and commercial or professional interests have  
116 driven overdiagnosis. (6, 18)

117 Consequences of overdiagnosis may be serious and can be subdivided in negative effects on  
118 patient health and additional costs within the health care system. (19) Health effects include  
119 impaired quality of life and early loss of life due to side-effects or complications of unnecessary  
120 subsequent testing or treatment. Incorrectly labeling of individuals as patients may also lead to  
121 stigmatization, impacting psychological well-being and indirectly exert social effects through  
122 eligibility for health benefits. In monetary terms, overdiagnosis can result in unwarranted usage  
123 of (follow-up) tests, treatment and healthcare facilities and services.

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3 124 Despite the increasing number of publications on overdiagnosis, ranging from discussions on  
4 125 overdiagnosis definition to estimating its impact, a systematic analysis on overdiagnosis is still  
5 126 lacking. In the present study, we provide a systematic overview of research that has been  
6 127 performed across medical disciplines surrounding the topic of overdiagnosis. Not only will we  
7 128 give insight into how and in what clinical fields overdiagnosis is studied, but also provide  
8 129 directions for further applied and methodological research to investigate the mechanisms and  
9 130 impact of overdiagnosis, and to generate directions for reducing or preventing overdiagnosis.

## 131 **Methods**

132 PubMed was systematically searched using keywords related to overdiagnosis, overdiagnosis  
133 and insignificant disease, by using the following query:

134 *overdiagnos\*[tw] OR over diagnos\*[tw] OR overdetect\*[tw] OR over detect\*[tw] OR "insignificant*  
135 *disease" OR overscreen\*[tw]*

136 These terms were chosen as they were believed to capture most concepts related to  
137 overdiagnosis, generating a representative set of articles. All English articles on humans where  
138 the full text was available were included. Articles in which overdiagnosis was a dominant theme  
139 were included. Overdiagnosis was considered a dominant theme when a paper clearly addressed  
140 overdiagnosis as an issue being investigated or discussed. For example, a study on the adoption  
141 of a new threshold guideline for PSA prostate cancer screening was considered to have a  
142 dominant overdiagnosis theme. In contrast, a study that used overdiagnosis as a buzzword and  
143 merely suggested in the discussion that overdiagnosis might possibly play a role or have  
144 occurred, was excluded. Studies with overdiagnosis as a dominant theme were included  
145 regardless of which definition of overdiagnosis the authors adopted.

146 The titles and abstracts of the included studies were then screened. Included studies were  
147 systematically assessed using (a list of) prespecified criteria. These criteria were established by  
148 screening the first 200 studies of the search query. They included clinical field, study aim, article  
149 type, type of diagnostic test, whether this was a screening test, and the context in which  
150 overdiagnosis was discussed. These are criteria are described below (see further details in the  
151 supplementary file). Articles were assessed based solely on title and abstract. If an abstract was  
152 unavailable (e.g. opinion pieces), the full text was scanned.

### 153 Clinical field

154 The clinical field to which the study belonged was determined using the ICD-10 classification.  
155 When a study addressed more than one clinical field or did not address overdiagnosis within a  
156 specific clinical field, but discussed overdiagnosis on a more general level, they were included in  
157 the separate category "No specific clinical field".



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3 158 Study aim  
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6 159 Two study aims were distinguished: 1) studies focusing on *how* overdiagnosis should be studied.  
7 160 These are studies with a methodological aim. Examples are studies looking into how  
8 161 overdiagnosis estimations are affected by the methods used, or studies providing a framework  
9 162 for the definition of overdiagnosis. Simulation studies using mathematical models for estimating  
10 163 the extent of overdiagnosis were also classified as methodological studies. Studies not  
11 164 addressing the aforementioned concepts, but rather provide, for example, a qualitative overview  
12 165 of the (possible) impact of overdiagnosis in a certain field, or calculate overdiagnosis estimates  
13 166 from empirical data, were considered to have 2) a non-methodological aim.  
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18 167 Article type  
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20 168 Studies were classified using four article types: primary studies, narrative reviews, systematic  
21 169 reviews or commentaries. Primary studies used data collected from trials, observational studies  
22 170 or generated using simulation models. Narrative reviews described a broad oversight on  
23 171 overdiagnosis. These included editorials, opinion pieces, interviews and overviews. Systematic  
24 172 reviews stated a specific hypothesis and tested this using a systematic approach to gather  
25 173 existing literature. If a systematic approach was lacking, these studies were scored as narrative  
26 174 reviews. Studies were considered commentaries when they, replied to previously published  
27 175 papers.  
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33 176 Type of diagnostic test  
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35 177 Diagnostic tests were categorized into six types: imaging, medical examination, biomarker,  
36 178 histology, prediction model or various. Whenever a study looked into a combination of two  
37 179 tests, both types were scored. For example, an image guided biopsy would be scored as both an  
38 180 imaging and histologic diagnostic test. If three or more diagnostic tests were addressed within a  
39 181 study, or overdiagnosis was addressed in a general context without any diagnostic test in  
40 182 particular, this was scored under "Various tests".  
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45 183 Screening  
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47 184 When studies focused on a test used for screening groups of asymptomatic individuals, this was  
48 185 scored as a screening study. Studies that did not explicitly state that the diagnostic test was  
49 186 studied in the context of screening, were scored as a non-screening.  
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52 187 Overdiagnosis context  
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54 188 To assess the context in which studies discussed overdiagnosis five categories were defined:  
55 189 estimating extent of overdiagnosis, disease definition, overdiagnosis communication, incidental  
56 190 findings, and genomics. The first category, estimating extent of overdiagnosis, relates to all  
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191 articles giving a quantified estimate of overdiagnosis. Disease definition revolves around the  
192 setting of thresholds to define the absence or presence of a disease or to distinguish between  
193 two subcategories of a certain disease (e.g. progressive and non-progressive forms).  
194 Overdiagnosis communication relates to studies aimed at assessing and improving the  
195 understanding of overdiagnosis in the general public, and improving overdiagnosis  
196 dissemination by the healthcare professionals. Studies addressing abnormalities found of an  
197 unrelated condition during either diagnostic testing or surgery were scored as studies on  
198 incidental findings. Spurious findings on genome wide screening tests were scored in the  
199 overdiagnosis context of genomics.

## 200 Results

201 The PubMed search resulted in a total number of 3802 studies identified. After application of the  
202 inclusion criteria 2829 studies were screened on title and abstract. Studies in which  
203 overdiagnosis was a dominant theme yielded 1457 studies. (Figure 1). Table 1 provides a  
204 summarized view of the characteristics of the total number of studies, the four largest clinical  
205 fields and studies not related to a specific clinical field.

206 *[insert Figure 1 approximately here]*

### 207 Clinical field

208 Papers on overdiagnosis were found in all clinical fields, but were mainly published within  
209 oncology (51%), in which breast (34%), prostate (18%) and lung cancer (15%) ranked as most  
210 prevalently studied. Other clinical fields addressing overdiagnosis included mental disorders  
211 (10%), infectious diseases (9%) and cardiovascular disease (6%). Within these fields, studies were  
212 predominantly looking into bipolar disorder, malaria and pulmonary embolism (PE), respectively.  
213 (20-25)

### 214 Study aim

215 Studies addressing methodological issues consisted of 21%. The majority of these studies were  
216 performed within the field of oncology. However, non-methodological studies were the most  
217 common study aim used across all clinical fields, accounting for 79% of the total number of  
218 articles. These notably included studies using empirical data to assess the occurrence or  
219 estimate overdiagnosis for a specific disease.

### 220 Article type

221 Primary studies (61%) were the most common article type discussing overdiagnosis. Of all  
222 included studies narrative, systematic reviews and commentaries represented 20%, 9% and 9%

223 respectively. From all studies that addressed a specific clinical field, the proportion of systematic  
224 reviews and commentaries was relatively high within oncology.

### 225 Type of diagnostic test

226 Imaging was the most often encountered diagnostic test, accounting for 32% of all studies.  
227 Biomarkers (18%), histology (16%) and medical examination (13%) were approximately equally  
228 often found. Prediction models were less common (3%). The proportion not related to one  
229 particular diagnostic test of interest was 18%. Distributions of diagnostic tests varied  
230 significantly depending on the clinical field. Imaging was most prevalent in oncology (47%),  
231 related to breast (55%) and lung cancer screening (23%). Within the field of mental disorders  
232 medical examination was often seen in the form of application of the DSM (Diagnostic and  
233 Statistical Manual of Mental Disorders) as diagnostic tool. Biomarkers and histology were seen  
234 relatively more frequent as diagnostic tests for infectious diseases when compared to other  
235 clinical fields.

### 236 Screening

237 Diagnostic testing was studied in the context of screening 42% of studies. There was however a  
238 skewed distribution between clinical fields. Within oncology, 74% of all studies were related to  
239 screening, whereas for mental disorders, infectious diseases and cardiovascular diseases this was  
240 11% or lower.

241 *[insert Table 1 approximately here]*

### 242 Overdiagnosis context

243 The context in which overdiagnosis was most frequently discussed related to its estimation  
244 (57%). Only within the field of mental disorders was disease definition more frequently discussed  
245 than overdiagnosis estimation (45% vs 25%). Descriptions and example studies on each of the  
246 five predefined categories can be found in table 2. The majority of studies discussing  
247 overdiagnosis (77%) were classifiable in one of these categories. Studies that did not fall within  
248 any of the five categories were scored in a separate "Other" category (23%). Results for each of  
249 these overdiagnosis contexts are discussed below.

250 *[insert table 2 approximately here]*

### 251 *Overdiagnosis estimation*

252 The most common context of discussion relates to overdiagnosis estimation, accounting for  
253 57% of all studies. These articles could be divided into two groups. The first were studies  
254 attempting to estimate the degree of overdiagnosis in their respective clinical fields. (78%) These

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2  
3 255 often described the impact of implementation or a threshold shift of a diagnostic or screening  
4 256 intervention on the rate of overdiagnosis. The second group represented studies that report  
5 257 methodological approaches for *how* one should estimate overdiagnosis. (22%) Differences  
6 258 regarding definitions used, measurement, study design and methods for estimation can lead to  
7 259 different results (31), hence there is often a large spread in these estimates, resulting in  
8 260 controversy regarding the true impact of overdiagnosis in the field.

### 13 261 *Disease definition*

15 262 In 16% of all studies disease definition was addressed. A relatively high proportion of these  
16 263 studies was addressed in the context of mental disorders (30%). Common topics included  
17 264 application of DSM for bipolar disorder, depression and ADHD. (32, 33) The other major  
18 265 contributor was in oncology (24%), where the main issue was the transition of benign to  
19 266 malignant growths. Examples of such pre-disease conditions are DCIS, early stage prostate  
20 267 tumors and papillary thyroid carcinoma. (34-36)

### 24 268 *Overdiagnosis communication*

27 269 Communication about overdiagnosis with patients or the public accounted for 3.0% of all 1457  
28 270 publications. This mainly involved the people's understanding of the concept of overdiagnosis,  
29 271 and whether they perceived it to be an issue. (28, 37, 38) Other articles dealt with  
30 272 communication of overdiagnosis between the patient and the treating physician, (39, 40) or the  
31 273 development and effectiveness of decision aids. (41, 42)

### 34 274 *Other contexts*

37 275 Scientific literature on overdiagnosis in genomics and incidental findings were found only  
38 276 sporadically (0.3% and 0.5%). One of the most commonly observed topics in the other category  
39 277 was drivers and consequences of overdiagnosis. (18, 19, 43, 44) These were often mentioned  
40 278 alongside in narrative reviews on overdiagnosis. Furthermore, trend studies were common,  
41 279 describing the possibility of overdiagnosis based on a rapid increase in the number of  
42 280 diagnoses, without any significant rise in the mortality rate. These studies did not provide an  
43 281 exact overdiagnosis estimate, but rather an indication that overdiagnosis might be occurring or  
44 282 increasing, based on historic data. Another context in which overdiagnosis was commonly  
45 283 addressed, especially in the last couple of years, was its definition. These studies aim at  
46 284 formulating accurate and appropriate definitions of overdiagnosis as well as related terminology  
47 285 (e.g. overmedicalisation, overdiagnosis, disease mongering). In addition, some have attempted  
48 286 defining broad overall classifications to provide guidance for distinction between different  
49 287 overdiagnosis subtypes. (13, 16)

## 57 288 **Discussion**

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3 289 This systematic review provides insight in the current landscape of overdiagnosis. There is great  
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5 290 diversity in study characteristics across medical disciplines and in the contexts in which  
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7 291 overdiagnosis is discussed. Some characteristics correlate with specific clinical fields, with, for  
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9 292 example, screening occurring predominantly in oncological studies and medical examination  
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11 293 being the most prevalently used diagnostic test for mental disorders. Overdiagnosis is discussed  
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13 294 in a wide array of contexts, however two could be distinguished which invoked significant  
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15 295 debate: 1) differences in overdiagnosis definition, 2) differences in methods used, leading to  
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17 296 varying overdiagnosis estimates, and 3) typologies for overdiagnosis.

### 16 297 Overdiagnosis definitions

18 298 The definition of overdiagnosis has been topic of discussion for some time. In a narrow sense it  
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20 299 refers to a diagnosis that does not result in a net benefit for an individual. (1) This can be viewed  
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22 300 within an individual or on a group level, where benefits (early detection of clinically relevant  
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24 301 disease) are weighted against the deficits (overdiagnosis and its associated consequences).  
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26 302 However, not all studies follow this definition, but rather describe overdiagnosis as a diagnosis  
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28 303 of a "disease" in an individual, that will never go on to cause symptoms or early death. (7) Using  
29  
30 304 this definition, overdiagnosis can occur only in asymptomatic individuals, implying that  
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32 305 overdiagnosis in most mental disorders is impossible (as virtually all of these deal with  
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34 306 symptomatic individuals). Others have used the relation between pathology and symptoms as a  
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36 307 measure of overdiagnosis. (45, 46) In the latter there is no doubt there is a clear abnormality,  
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38 308 however it is uncertain whether smaller forms of this abnormality still significantly correlate with  
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40 309 future clinically relevant disease. Ultimately, the question would be how or even if we should  
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42 310 treat these individuals. These examples of definitions demonstrate the heterogeneity and  
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44 311 complexity of the concept of overdiagnosis, and have led to the discussion regarding the extent  
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46 312 or even the existence of overdiagnosis.

### 40 313 Methods for overdiagnosis estimation

43 314 Another discussion revolves around variation in estimates of overdiagnosis. Major trials such as  
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45 315 the European Randomized Study of Screening for Prostate Cancer (ERSPC), the National Lung  
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47 316 Screening Trial (NLST), the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial,  
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49 317 and the Malmö breast cancer screening trial, often form the basis for these discussions. (47-50)  
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51 318 These trials look into the effects of cancer screening programs. The ERSPC did not provide an  
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53 319 overdiagnosis in prostate cancer screening in their initial publication (51), but did provide an  
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55 320 estimate of 41% in their 2014 publication. (47) However, this was obtained through modelling,  
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57 321 and not calculated directly from the observed data. The NLST merely states that overdiagnosis is  
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59 322 presumably not large, as the number of breast cancers diagnosed between the two screening  
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323 arms is comparable. (48) And the PLCO and Malmö breast cancer screening trials did not state  
324 anything about overdiagnosis. (49, 50) The scientific community reacted by using different

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3 325 methods to provide overdiagnosis estimates for these trials. The rate of overdiagnosis that is  
4 326 estimated depends on various features such as the definitions and measurements used, study  
5 327 design and context and estimation approaches applied. (12, 31, 52-56) The latter can be divided  
6 328 in lead-time (the time between screening detection and clinical presentation) and excess  
7 329 incidence approach (excess number of cases between a screening and non-screening group),  
8 330 each of which has its merits and issues, and requires assumptions to be made. Ultimately, the  
9 331 variety in methodology used has resulted in variation in overdiagnosis estimates, and significant  
10 332 controversy between studies. (11, 56, 57)

### 16 333 Overdiagnosis typologies

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18 334 Several studies have provided overviews and acknowledged that finding a singular definition of  
19 335 overdiagnosis may not be feasible. However providing an overdiagnosis classification, aimed at  
20 336 describing subtypes of overdiagnosis, could prove to be useful. Some efforts have been made to  
21 337 create such a typology, however this is challenging as definitions vary widely and classifications  
22 338 can be made over different axes. Hence, this is a complex issue which should be addressed in a  
23 339 systematic manner. A comprehensive typology could aid researchers in their communication as  
24 340 was already suggested in a paper by Moynihan et al in 2012. (6) A recent paper by Rogers  
25 341 described the use of maldetection (issues with our understanding of what 'truly' disease is) and  
26 342 misclassification (an implicit or explicit threshold shift resulting in overdiagnosis). (13) Shortly  
27 343 after, Carter et al described the concepts of predatory, tragic and misdirected overdiagnosis. (17)  
28 344 Other work by Hofmann et al takes a more sociological and philosophical point of view. In their  
29 345 most recent publication, they use indicative, measurable and observable phenomena to describe  
30 346 the different stages in which a phenomenon develops into a clinical manifestation. (16) In  
31 347 oncology a tumor-patient classification has been described, relating to tumors that are  
32 348 regressive, non-progressive or truly malignant disease. (58) Although these works provide great  
33 349 improvement in our understanding of the issues at hand, they do not give further guidance as  
34 350 to how these concepts should be used in clinical research.

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36  
37 351 To our knowledge, this is the first scoping review performed on the subject of overdiagnosis. It  
38 352 provides broad insight in the available research on specific topics within overdiagnosis. To  
39 353 appreciate the findings in this review, the following limitations should be considered. First,  
40 354 studies were excluded when they did not have full text available. This may have led to exclusion  
41 355 of a minor selection of relevant articles, but not a systematic exclusion of a particular range of  
42 356 overdiagnosis studies. The issue in identifying studies discussing overdiagnosis, is that there are  
43 357 no clear selection criteria to find these. Terminologies used to describe overdiagnosis differ  
44 358 between studies, are widely spread and search filters in medical databases are lacking. Hence,  
45 359 our goal was not to perform a comprehensive search. Instead, we aimed at finding a large  
46 360 representative of papers discussing overdiagnosis.

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3 361 Second, unexpectedly, studies on genomics and incidental findings (or incidentalomas) were  
4 362 largely missed. Forward reference checking revealed that some of the papers not found in our  
5 363 search may use other terminology for describing overdiagnosis, such as the “prevalence of  
6 364 significant findings” or “diagnostic value”. Using our search strategy these articles were  
7 365 unfortunately omitted and not included in this review. When researchers are interested  
8 366 particularly in this subset, the information in this review might not suffice..

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13 367 A third limitation relates to the lack of specific search terms for overtesting and overutilization.  
14 368 These are concepts closely related to overdiagnosis, describing the use of a test when there is  
15 369 no indication to do so. (59) In this review, these were not included in the search query, which  
16 370 may have led to selection in our dataset. However, although overtesting and overutilization may  
17 371 ultimately lead to overdiagnosis, this does not necessarily have to be the case. False-positives,  
18 372 resource waste and additional costs are consequences frequently associated with these  
19 373 concepts, and definition papers do not address overtesting as a separate subset in the spectrum  
20 374 of “Too much medicine”. (1)

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25 375 In summary, overdiagnosis is a topic discussed over medical disciplines, and in a wide array of  
26 376 contexts, from conceptual ideas in definition to practical issues for clinicians in daily practice.  
27 377 The various characteristics of studies looking at overdiagnosis suggest that there may be  
28 378 different (and sometimes multiple) underlying mechanisms through which it may manifest itself.  
29 379 Clarity on these mechanisms will aid researchers communicate their results, especially with  
30 380 regard to overdiagnosis estimates. Future methodological studies should focus on establishing a  
31 381 framework to aid clinicians and researchers in understanding the different subtypes of  
32 382 overdiagnosis, their consequences, and provide guidance for selecting appropriate study  
33 383 designs and methods that match the research question of interest.

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12 402 *organisations that might have an interest in the submitted work in the previous three years, no other*  
13 403 *relationships or activities that could appear to have influenced the submitted work.*  
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22 409 *KGMM, LH and CAN all have approved the final version to be published, and its accuracy and integrity.*  
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25 410 **Data sharing statement**  
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27 411 *Additional data is available by contacting the first author through the corresponding email address*  
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Figure 1. Flow-diagram of article selection for further review and scoring

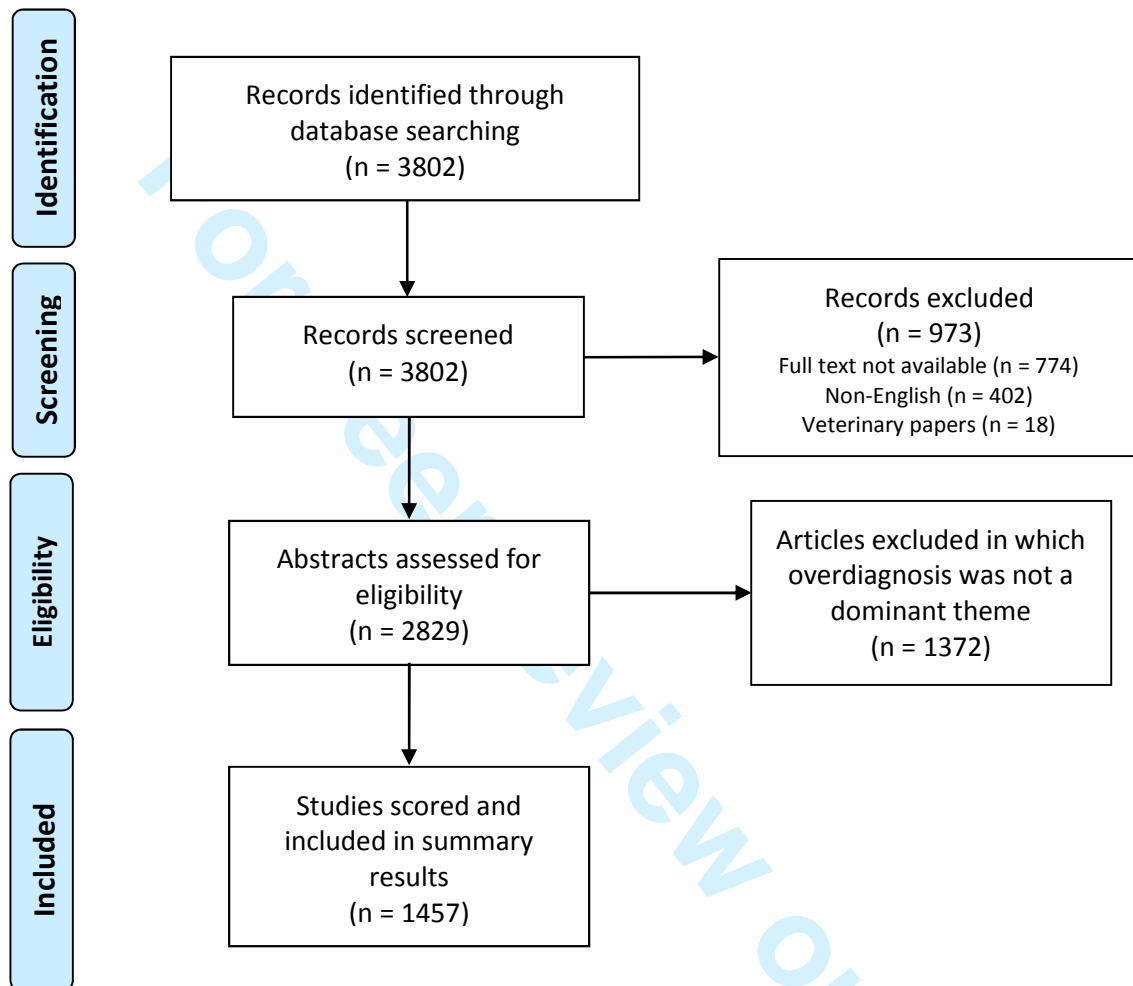


Table 1. Characteristics of papers in which overdiagnosis was a dominant theme. Results are shown for the total number of articles, the four largest clinical fields and studies not addressing a specific clinical field

	<b>Total</b> <b>(n =1457)</b>	<b>Oncological</b> <b>disorders</b> <b>(n = 742)</b>	<b>Mental</b> <b>disorders</b> <b>(n =150)</b>	<b>Infectious</b> <b>diseases</b> <b>(n = 124)</b>	<b>Cardiovascular</b> <b>disorders</b> <b>(n = 84)</b>	<b>No specific</b> <b>clinical field</b> <b>(n = 54)</b>
<b>Study aim</b>						
Methodological	<b>21%</b>	33%	11%	4%	11%	41%
Non-methodological	<b>79%</b>	67%	89%	96%	89%	59%
<b>Article type</b>						
Primary study	<b>61%</b>	56%	55%	83%	64%	28%
Narrative review	<b>20%</b>	19%	30%	10%	21%	52%
Systematic review	<b>9%</b>	12%	7%	0.8%	11%	17%
Commentary	<b>9%</b>	13%	8%	6%	4%	4%
<b>Diagnostic test</b>						
Imaging	<b>32%</b>	47%	4%	5%	45%	9%
Medical examination	<b>18%</b>	2%	60%	28%	26%	9%
Biomarker	<b>16%</b>	18%	3%	25%	12%	4%
Histology	<b>13%</b>	17%	0%	20%	2%	2%
Prediction model	<b>3%</b>	4%	0.6%	2%	2%	2%
Various	<b>18%</b>	13%	32%	20%	13%	74%
<b>Screening</b>						
Yes	<b>42%</b>	74%	5%	6%	11%	24%
No	<b>58%</b>	26%	95%	94%	89%	76%
<b>Overdiagnosis context</b>						
Overdiagnosis estimation	<b>57%</b>	61%	25%	60%	68%	37%
Disease definition	<b>16%</b>	8%	45%	15%	15%	15%
Overdiagnosis communication	<b>3%</b>	5%	2%	0,8%	0%	4%
Incidental findings	<b>1%</b>	0.5%	0%	0%	0%	2%
Genomics	<b>0.3%</b>	0.3%	0%	0%	1%	4%
Other*	<b>23%</b>	26%	28%	24%	15%	39%

\*Subcategories in this category include: overdiagnosis definition, drivers and consequences of overdiagnosis and trend studies suggesting overdiagnosis

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Table 2. Descriptions and examples of context of overdiagnosis discussion

<b>Overdiagnosis context</b>	<b>Description</b>	<b>Example</b>	<b>Ref.</b>
Overdiagnosis estimation	Providing a quantitative estimate of overdiagnosis	<i>Estimation of overdiagnosis in low-dose computed tomography screening for lung cancer</i>	(26)
Disease definition	Setting thresholds to define the absence or presence of a disease, or distinguishing between two subcategories within a disease	<i>Current definitions of airflow obstruction and COPD yield overdiagnosis in primary care</i>	(27)
Overdiagnosis communication	Assessing and improving the understanding of overdiagnosis in the general public, and improving overdiagnosis dissemination by the healthcare professionals	<i>Assessing what the general public thinks is meant by the term 'overdiagnosis'</i>	(28)
Incidental findings	An abnormality found of an unrelated condition during either diagnostic testing or surgery	<i>Relevance of incidental findings when screening for a disorder in the abdominal area using multi-detector contrast-enhanced CT</i>	(29)
Genomics	Spurious genetic abnormalities	<i>Implications of genetic screening for common cancers in children</i>	(30)



Criteria for scoring (title and abstract)		
Criterion	Outcome	Description
Full-text available	Yes / No	Is a full-text available from pubmed?
Veterinary study	Yes / No	Is the paper a study with animals?
Overdiagnosis as a dominant theme	Yes / No	Is overdiagnosis discussed as a specific dominant theme <b>Include:</b> Prognostic / prediction studies relating to disease progression <b>Include:</b> Trend studies. Index test will often be not addressed <b>Include:</b> Active surveillance studies that assess what the impact is of having a in-between category, next to treat and do not treat <b>Exclude:</b> Studies in which no diagnostic method is evaluated <b>Exclude:</b> Erratums <b>Exclude:</b> Case-studies (n = < 10) <b>Exclude:</b> Overview articles without a specific focus on diagnostics <b>Exclude:</b> Articles not mentioning overdiagnosis or only briefly commenting on it (particularly in the discussion) Example: Exclude article which states: "When Diagnostic test X is replaced with Diagnostic test Y sensitivity and specificity may be improved. As a result overdiagnosis of Disease Z may be reduced"
Clinical field	Bone & connective tissue	Examples: Myopathy, osteoporosis, dental problems
	Cancer	Examples: Prostate cancer, breast cancer, leukemia <b>Exclude:</b> cervical cancer caused by HPV (=infection)
	Cardiovascular	Examples: Pulmonary embolism, angina
	Congenital	Examples: Down syndrome, hypospadias
	Ear	Example: Tinnitus
	Eye	Example: Juncetivitis
	Gastrointestinal	Examples: Crohn's disease, reflux disease, liver failure
	Gynaecology & Obstetrics	Example: Preeclampsia
	Immune system	Examples: Allergic reactions, autoimmune disorders, Heparin induced thrombocytopenia (HIT), PANDA's, Rheumatoid arthritis
	Infection	Examples: Malaria, HIV, HPV, Clostridium difficile, pneumonia
	Mental	Examples: ADHD, autism, depression, schizophrenia, bipolar disorder, (vascular) dementia <b>Include:</b> Diseases that are primarily psychiatric disorders and often result in impaired cognitive function <b>Exclude:</b> See neurological disorders
	Metabolic	Examples: Diabetes, hypogonadism, hypothyroidism, growth related 'disorders', nutrition status
	Neurological	Example: Multiple sclerosis, Parkinsons, Alzheimer <b>Include:</b> Diseases of the central / peripheral nervous system, that often have motorical implications <b>Exclude:</b> See mental disorders
	Perinatal	Example: Malnutrition of the unborn child, child specific problems during pregnancy <b>Include:</b> disease in the unborn child
Respiratory	Examples: COPD, asthma, nasal disorders	
Skin	Example: Eczema	
Trauma	Examples: Car accidents, cuts, fractures, sprains, injury during surgery	
Urogenital	Examples: Chronic kidney failure, kidney stones	
No specific clinical field	Multiple clinical domains are assessed <b>OR</b> it is unclear if the paper focusses on a specific clinical domains Example: a methodological paper on how we should quantify overdiagnosis	
Study aim	Methodological	Papers describing a theoretical framework for assessing overdiagnosis <b>Include:</b> Commentaries discussing the way overdiagnosis was determined in a different empirical primary study <b>Include:</b> Combination papers; Papers that are empirical, but also have a strong methodological focus on overdiagnosis <b>Include:</b> Modelling studies
	Non-methodological	Results from a primary study or assessment of outcomes by a review / overview paper
Article type	Commentary	A comment, reply or rebuttal on a previously published paper or commentary
	Narrative review	A paper giving a broad oversight of a specific topic, often from one particular authors view <b>Include:</b> editorials <b>Include:</b> opinion pieces <b>Include:</b> interviews <b>Include:</b> guidelines <b>Exclude:</b> Overviews that only refer to 1 or 2 accuracy studies, without further discussion on the topic of overdiagnosis
	Primary paper	Consists of a collection of original primary data collected by the researcher
	Systematic review	Collection and synthesis of available evidence on a topic. <b>Include:</b> Systematic assessments / meta-analyses of various articles within a specific domain <b>Exclude:</b> General discussions and exposes about a subject without a clear structural approach
Type of diagnostic test	Biomarker	Any measurement of chemicals in the human body as well as genotyping <b>Include:</b> immunohistochemistry (even though this may be assessed via microscopy in some cases) <b>Include:</b> Rapid diagnostic test for malaria
	Histology	Qualitative visual assessment of a target tissue through biopsy under a microscope (or similar devices) <b>Exclude:</b> Rapid diagnostic test for malaria (biomarker) <b>Exclude:</b> Scopy's (medical examination)
	Imaging	Any form of digital visualisation of the human body, such as MRI, CT, EKG, EEG, etc <b>Exclude:</b> Scopy's (medical examination)
	Medical examination	(Quick) medical tests that are performed directly by the clinician, either with or without specific medical equipment <b>Include:</b> Endoscopy, coloscopy, spirometry, reflex test, exploratory surgery, DSM-V assessment, psychological evaluations, skin prick tests (for allergy), blood pressure measurement <b>Include:</b> Assessment of medical history of the patient by a clinician, such as age, gender, smoking habits, exercise pattern, etc
	Prediction model	List of predictors used in a prediction model <b>Exclude:</b> Overall assessments using multiple tests (= "none") <b>Exclude:</b> Modelling studies that evaluate one particular index test, while using input on transition predictions in the rest of that model <b>Note:</b> Other index tests can not be checked with a prediction model, since they will be part of that model
	None	Not one specific test is studied (so a broad range of tests or no specific one is addressed) <b>Include:</b> Overview papers that only discuss the general topic of overdiagnosis <b>Include:</b> Papers discussing various tests (hence there is no specific index test)

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Screening	Yes / No	<p>Is the primary focus of the study on diagnosis or detection in asymptomatic patients?</p> <p><b>Include:</b> Screening is mentioned multiple times and explicitly</p> <p><b>Exclude:</b> Screening as an example in an overview / review paper</p> <p><b>Exclude:</b> Prognostic studies in patients that already received diagnosis</p>
Overdiagnosis context	Overdiagnosis estimation	<p>Overdiagnosis relating to the effect that a diagnostic test has on the number of excess cases found</p> <p><b>Include:</b> Overdiagnosis mentioned in the results</p> <p><b>Include:</b> Accuracy studies quantifying false-positive findings or % of overdiagnosis</p> <p><b>Include:</b> Modelling papers that quantify overdiagnosis</p> <p><b>Exclude:</b> Comparison of two diagnostic tests, without <b>explicit</b> quantification / assessment of overdiagnosis</p> <p><b>Exclude:</b> Misdiagnosis / misclassification (= disease definition)</p> <p><b>Exclude:</b> Overview papers that only briefly mention results from other primary studies</p> <p><b>Exclude:</b> Overview papers that mention some quantitative results of overdiagnosis, but predominantly have a more broad discussion in general (=other)</p>
	Disease definition	<p>Overdiagnosis as a result of shifting the disease definition in terms of biomarker threshold or criteria in a scoring list</p> <p><b>Include:</b> Misclassification / misdiagnosis</p> <p><b>Include:</b> Papers assessing pathologic / biologic / mechanistic background of the disease in context with overdiagnosis. <i>However be critical whether these directly link particular biologic subclassifications of a disease to overdiagnosis</i></p>
	Overdiagnosis communication	<p>Overdiagnosis as subject of communication between clinicians and/or patients</p> <p><b>Include:</b> Studies that assess overdiagnosis communication to patients before or after diagnostic tests</p> <p><b>Include:</b> Studies assessing people's general understanding of the concept of overdiagnosis</p>
	Incidental findings	<p>Overdiagnosis as a coincidental finding resulting from diagnostic testing of an unrelated illness</p>
	Genomics	<p>Overdiagnosis resulting from genome (screening) assessments, determining high-risk groups</p>
Other	<p>Overdiagnosis that can not be related to any of the categories above</p> <p><b>Include:</b> Overview paper describing multiple aspects of overdiagnosis (e.g. accuracy, definition, litigation, methodology)</p> <p><b>Include:</b> Studies looking at the downstream consequences of overdiagnosis (e.g. quality of life)</p> <p><b>Include:</b> Studies looking at overall reasons for clinicians to overdiagnose (e.g. litigation risk, carefullness, unaware of negative consequences)</p> <p><b>Include:</b> Trend studies</p> <p><b>Include:</b> Studies on drivers and consequences of overdiagnosis</p>	

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# BMJ Open

## Overdiagnosis across medical disciplines: a scoping review

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3 **1 Title**

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1  
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3 **Abstract**  
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5  
6 **Objective** To provide insight into how and in what clinical fields overdiagnosis is studied, and  
7 give directions for further applied and methodological research.  
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9  
10 **Design** Scoping review

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12 **Data sources** Medline up to August 2017

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14 **Study selection** All English studies on humans, in which overdiagnosis was discussed as a  
15 dominant theme.  
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17  
18 **Data extraction** Studies were assessed on clinical field, study aim (i.e. methodological or non-  
19 methodological), article type (e.g. primary study, review), the type and role of diagnostic test(s)  
20 studied, and the context in which these studies discussed overdiagnosis.  
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23  
24 **Results** From 4896 studies, 1851 were included for analysis. Half of all studies on overdiagnosis  
25 were performed in the field of oncology (50%). Other prevalent clinical fields included mental  
26 disorders, infectious diseases and cardiovascular diseases accounting for 9%, 8% and 6% of  
27 studies respectively. Overdiagnosis was addressed from a methodological perspective in 20% of  
28 studies. Primary studies were the most common article type (58%). The type of diagnostic tests  
29 most commonly studied were imaging tests (32%), although these were predominantly seen in  
30 oncology and cardiovascular disease (84%). Diagnostic tests were studied in a screening setting  
31 in 43% of all studies, but as high as 75% of all oncological studies. The context in which studies  
32 addressed overdiagnosis related most frequently to its estimation, accounting for 53%.  
33 Methodology on overdiagnosis estimation and definition provided a source for extensive  
34 discussion. Other contexts of discussion included definition of disease, overdiagnosis  
35 communication, trends in increasing disease prevalence, drivers and consequences of  
36 overdiagnosis, incidental findings and genomics.

37  
38 **Conclusions** Overdiagnosis is discussed across virtually all clinical fields and in different  
39 contexts. The variability in characteristics between studies and lack of consensus on  
40 overdiagnosis definition indicate the need for a uniform typology to improve coherence and  
41 comparability of studies on overdiagnosis.  
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3 40 **Strengths and limitations of this study**  
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- 6 41 - First complete overview of overdiagnosis across medical disciplines  
7 42 - Identification of the dominant clinical fields in which overdiagnosis is being studied, what  
8 43 characteristics these papers have, and in what context it is being studied  
9  
10 44 - Not a fully comprehensive systematic review, due to widespread variation in terminology  
11 45 and concepts used related to overdiagnosis  
12  
13 46 - Studies on incidental findings were likely missed due to usage of different terminology  
14 47 to describe overdiagnosis  
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## 49 Introduction

50 Overmedicalisation is the broad overarching term describing the use of “too much medicine”. (1)  
51 It encompasses various concepts such as disease mongering, misdiagnosis, overutilization,  
52 overdiagnosis and overtreatment. Initiatives relating to these concepts have begun to flourish  
53 on a global scale under the ‘Choosing Wisely’ initiative and in national programs such as Slow  
54 Medicine (Italy, the Netherlands and Brazil), Quaternary Prevention (Belgium) and Do not do  
55 (UK). (2, 3) A subcategory of the aforementioned concepts is overdiagnosis. This has become an  
56 even more popular term especially over the last two decades. (4-9) Furthermore, an annual  
57 conference going by the name of “Preventing Overdiagnosis”, dedicated to issues surrounding  
58 this concept, has been gaining popularity ever since its start in 2013, demonstrating a growing  
59 interest in the topic. (10) In this scoping review we will focus specifically on overdiagnosis.

60 Defining overdiagnosis is challenging and diverse definitions exist. (11, 12) In a narrow sense,  
61 overdiagnosis describes individuals receiving a diagnosis with a condition that would never have  
62 become symptomatic before the end of the individual’s life. (5, 7) However, overdiagnosis has  
63 also been described as giving a diagnosis that would not yield a net benefit. (1) These  
64 definitions are not similar, and thus may lead to different interpretations of (the extent of)  
65 overdiagnosis. Consequently, the mechanisms leading to overdiagnosis may also differ. Labeling  
66 an individual with a blood pressure over a certain threshold as hypertensive, and thus  
67 “diseased”, is conceptually different than not knowing whether one should diagnose an  
68 individual with a very small potentially malignant growth as having cancer, and thus “diseased”.  
69 Providing definitions in combination with mechanisms of overdiagnosis for a typology is  
70 challenging and source of extensive discussion. (13-17)

71 The range of overdiagnosis drivers is also extensive. It, amongst others, includes technological  
72 developments that detect smaller abnormalities than ever before which might not become  
73 clinically manifest. Furthermore, the use of large scale screening programs, inappropriate  
74 application of diagnostic criteria, legal incentives, cultural beliefs (i.e. that we should do  
75 everything in our power to find and treat disease) and commercial or professional interests have  
76 driven overdiagnosis. (6, 18-20)

77 Consequences of overdiagnosis may be serious and can be subdivided in negative effects on  
78 patient health and additional costs within the health care system. (21) Health effects include  
79 impaired quality of life and early loss of life due to side-effects or complications of unnecessary  
80 subsequent testing or treatment. Incorrectly labeling of individuals as patients may also lead to  
81 stigmatization, impacting psychological well-being and indirectly exert social effects through  
82 eligibility for health benefits. In monetary terms, overdiagnosis can result in unwarranted usage  
83 of (follow-up) tests, treatment and healthcare facilities and services.

84 Despite the increasing number of publications on overdiagnosis, ranging from discussions on  
85 overdiagnosis definition to estimating its impact, a scoping analysis on overdiagnosis is still  
86 lacking. In the present study, we provide an overview of research that has been performed  
87 across medical disciplines surrounding the topic of overdiagnosis. Not only will we give insight  
88 into how and in what clinical fields overdiagnosis is studied, but also provide directions for  
89 further applied and methodological research to investigate the mechanisms and impact of  
90 overdiagnosis, and to generate directions for reducing or preventing overdiagnosis.

## 91 **Methods**

92 PubMed was searched on August 2017 for published articles using keywords related to  
93 overdiagnosis, overdetection, overscreening, insignificant disease, overtesting,  
94 overmedicalisation, pseudodisease, inconsequential disease, and quaternary prevention, by  
95 using the following query:

96 *overdiagnos\*[tw] OR over diagnos\*[tw] OR overdetect\*[tw] OR over detect\*[tw] OR "insignificant*  
97 *disease"[tw] OR overscreen\*[tw] OR over screen\*[tw] OR overtest\*[tw] OR over test\*[tw] OR*  
98 *overmedical\*[tw] OR over medical\*[tw]OR "pseudodisease"[tw] OR "pseudo disease"[tw] OR*  
99 *"inconsequential disease"[tw] OR "Quaternary prevention"[tw]*

100 These terms were chosen as they were believed to capture most concepts related to  
101 overdiagnosis, generating a representative set of articles. All English articles on humans where  
102 the full text was available were included. Articles in which overdiagnosis was a dominant theme  
103 were included. Overdiagnosis was considered a dominant theme when a paper clearly addressed  
104 overdiagnosis as an issue being investigated or discussed. For example, a study on the adoption  
105 of a new threshold guideline for PSA prostate cancer screening was considered to have a  
106 dominant overdiagnosis theme. In contrast, a study that used overdiagnosis as a buzzword and  
107 merely suggested in the discussion that overdiagnosis might possibly play a role or have  
108 occurred, was excluded. Studies with overdiagnosis as a dominant theme were included  
109 regardless of which definition of overdiagnosis the authors adopted.

110 The titles and abstracts of the included studies were then screened. Included studies were  
111 assessed using (a list of) prespecified criteria. These criteria were established by screening the  
112 first 200 studies of the search query. They included clinical field, study aim, article type, type of  
113 diagnostic test, whether this was a screening test, and the context in which overdiagnosis was  
114 discussed. These criteria are described below (see further details in the supplementary file).  
115 Articles were assessed based solely on title and abstract. If an abstract was unavailable (e.g.  
116 opinion pieces), the full text was scanned.

### 117 Clinical field



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3 118 The clinical field to which the study belonged was determined using the ICD-10 classification.  
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5 119 When a study addressed more than one clinical field or did not address overdiagnosis within a  
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7 120 specific clinical field, but discussed overdiagnosis on a more general level, they were included in  
8  
9 121 the separate category "No specific clinical field".

#### 10 122 Study aim

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12 123 Two study aims were distinguished: 1) studies focusing on *how* overdiagnosis should be studied.  
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14 124 These are studies with a methodological aim. Examples are studies looking into how  
15  
16 125 overdiagnosis estimations are affected by the methods used, or studies providing a framework  
17  
18 126 for the definition of overdiagnosis. Simulation studies using mathematical models for estimating  
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20 127 the extent of overdiagnosis were also classified as methodological studies. Studies not  
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22 128 addressing the aforementioned concepts, but rather provide, for example, a qualitative overview  
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24 129 of the (possible) impact of overdiagnosis in a certain field, or calculate overdiagnosis estimates  
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26 130 from empirical data, were considered to have 2) a non-methodological aim.

#### 27 131 Article type

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29 132 Studies were classified using four article types: primary studies, narrative reviews, systematic  
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31 133 reviews or commentaries. Primary studies used data collected from trials, observational studies  
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33 134 or generated using simulation models. Narrative reviews described a broad oversight on  
34  
35 135 overdiagnosis. These included editorials, opinion pieces, interviews and overviews. Systematic  
36  
37 136 reviews stated a specific hypothesis and tested this using a systematic approach to gather  
38  
39 137 existing literature. If a systematic approach was lacking, these studies were scored as narrative  
40  
41 138 reviews. Studies were considered commentaries when they, replied to previously published  
42  
43 139 papers.

#### 44 140 Type of diagnostic test

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46 141 Diagnostic tests were categorized into six types: imaging, medical examination, biomarker,  
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48 142 histology, prediction model or various. Whenever a study looked into a combination of two  
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50 143 tests, both types were scored. For example, an image guided biopsy would be scored as both an  
51  
52 144 imaging and histologic diagnostic test. If three or more diagnostic tests were addressed within a  
53  
54 145 study, or overdiagnosis was addressed in a general context without any diagnostic test in  
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56 146 particular, this was scored under "Various tests".

#### 57 147 Screening

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59 148 When studies focused on a test used for screening groups of asymptomatic individuals, this was  
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149 scored as a screening study. Studies that did not explicitly state that the diagnostic test was  
150  
studied in the context of screening, were scored as a non-screening.

## 151 Overdiagnosis context

152 To assess the context in which studies discussed overdiagnosis five categories were defined:  
153 estimating extent of overdiagnosis, disease definition, overdiagnosis communication, incidental  
154 findings, and genomics. The first category, estimating extent of overdiagnosis, relates to all  
155 articles giving a quantified estimate of overdiagnosis. Disease definition revolves around the  
156 setting of thresholds to define the absence or presence of a disease or to distinguish between  
157 two subcategories of a certain disease (e.g. progressive and non-progressive forms).  
158 Overdiagnosis communication relates to studies aimed at assessing and improving the  
159 understanding of overdiagnosis in the general public, and improving overdiagnosis  
160 dissemination by the healthcare professionals. Studies addressing abnormalities found of an  
161 unrelated condition during either diagnostic testing or surgery were scored as studies on  
162 incidental findings. Spurious findings on genome wide screening tests were scored in the  
163 overdiagnosis context of genomics.

## 164 **Results**

165 The PubMed search resulted in a total number of 4896 studies identified. After application of the  
166 inclusion criteria 3746 studies were assessed for eligibility on title and abstract. Studies in which  
167 overdiagnosis was a dominant theme yielded 1851 studies. (Figure 1). Table 1 provides a  
168 summarized view of the characteristics of the total number of studies, the four largest clinical  
169 fields, all other remaining clinical domains and studies not related to a specific clinical field.

170 *[insert Figure 1 approximately here]*

### 171 Clinical field

172 Papers on overdiagnosis were found in all clinical fields, but were mainly published within  
173 oncology (50%), in which breast (34%), prostate (24%) and lung cancer (14%) ranked as most  
174 prevalently studied. Other clinical fields addressing overdiagnosis included mental disorders  
175 (9%), infectious diseases (8%) and cardiovascular disease (6%). Within these fields, studies were  
176 predominantly looking into bipolar disorder, malaria and pulmonary embolism (PE), respectively.  
177 (22-27)

### 178 Study aim

179 Studies addressing methodological issues consisted of 20%. The majority of these studies were  
180 performed within the field of oncology. However, non-methodological studies were the most  
181 common study aim used across all clinical fields, accounting for 80% of the total number of  
182 articles. These notably included studies using empirical data to assess the occurrence or  
183 estimate overdiagnosis for a specific disease.

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3 184 Article type  
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6 185 Primary studies (58%) were the most common article type discussing overdiagnosis. Of all  
7 186 included studies narrative, systematic reviews and commentaries represented 24%, 9% and 9%  
8 187 respectively. From all studies that addressed a specific clinical field, the proportion of systematic  
9 188 reviews and commentaries was relatively high within oncology.  
10  
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12 189 Type of diagnostic test  
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14 190 Imaging was the most often encountered diagnostic test, accounting for 32% of all studies.  
15 191 Biomarkers (15%), histology (13%) and medical examination (17%) were approximately equally  
16 192 often found. Prediction models were less common (3%). The proportion not related to one  
17 193 particular diagnostic test of interest was 21%. Distributions of diagnostic tests varied  
18 194 significantly depending on the clinical field. Imaging was most prevalent in oncology where it  
19 195 accounted for 48% of diagnostic tests, mostly related to breast (53%) and lung cancer screening  
20 196 (21%). Within the field of mental disorders medical examination was often seen in the form of  
21 197 application of the DSM (Diagnostic and Statistical Manual of Mental Disorders) as diagnostic  
22 198 tool. Biomarkers and histology were seen relatively more frequent as diagnostic tests for  
23 199 infectious diseases when compared to other clinical fields.  
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30 200 Screening  
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32 201 Diagnostic testing was studied in the context of screening in 43% of studies. There was however  
33 202 a skewed distribution between clinical fields. Within oncology, 75% of all studies were related to  
34 203 screening, whereas for mental disorders, infectious diseases and cardiovascular diseases this was  
35 204 15% or lower.  
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Table 1. Characteristics of papers in which overdiagnosis was a dominant theme. Results are shown for the total number of articles, the four largest clinical fields and studies not addressing a specific clinical field

	<b>Total</b> <b>(n =1851)</b>	<b>Oncological</b> <b>disorders</b> <b>(n = 920)</b>	<b>Mental</b> <b>disorders</b> <b>(n =171)</b>	<b>Infectious</b> <b>diseases</b> <b>(n = 143)</b>	<b>Cardiovascular</b> <b>disorders</b> <b>(n = 105)</b>	<b>Other clinical</b> <b>fields</b> <b>(n = 390)</b>	<b>No specific</b> <b>clinical field</b> <b>(n = 122)</b>
<b>Study aim</b>							
Methodological	<b>20%</b>	30%	11%	4%	10%	4%	34%
Non-methodological	<b>80%</b>	70%	89%	96%	90%	96%	66%
<b>Article type</b>							
Primary study	<b>58%</b>	55%	53%	85%	61%	69%	27%
Narrative review	<b>24%</b>	22%	32%	9%	24%	22%	52%
Systematic review	<b>9%</b>	12%	8%	1%	10%	5%	11%
Commentary	<b>9%</b>	11%	8%	6%	6%	4%	10%
<b>Diagnostic test</b>							
Imaging	<b>32%</b>	48%	3%	4%	47%	19%	7%
Medical examination	<b>17%</b>	3%	58%	26%	26%	30%	4%
Biomarker	<b>15%</b>	16%	3%	29%	10%	16%	3%
Histology	<b>13%</b>	17%	0%	21%	2%	11%	2%
Prediction model	<b>3%</b>	4%	1%	2%	3%	4%	1%
Various	<b>21%</b>	13%	35%	18%	12%	20%	84%
<b>Screening</b>							
Yes	<b>43%</b>	75%	5%	10%	15%	10%	20%
No	<b>57%</b>	25%	95%	90%	85%	90%	80%
<b>Overdiagnosis context</b>							
Overdiagnosis estimation	<b>53%</b>	57%	22%	63%	65%	60%	16%
Disease definition	<b>15%</b>	8%	46%	13%	14%	22%	8%
Overdiagnosis communication	<b>3%</b>	5%	2%	0.7%	0%	0.8%	3%
Incidental findings	<b>0.8%</b>	0.8%	0%	0%	1%	1%	2%
Genomics	<b>0.4%</b>	0.3%	0%	0%	1%	0%	3%
Other*	<b>28%</b>	29%	30%	24%	19%	16%	67%

\*Subcategories in this category include: overdiagnosis definition, drivers and consequences of overdiagnosis and trend studies suggesting overdiagnosis

## 205 Overdiagnosis context

206 The context in which overdiagnosis was most frequently discussed related to its estimation  
 207 (53%). Only within the field of mental disorders was disease definition more frequently discussed  
 208 than overdiagnosis estimation (46% vs 22%). Descriptions and example studies on each of the  
 209 five predefined categories can be found in table 2. The majority of studies discussing  
 210 overdiagnosis (72%) were classifiable in one of these categories. Studies that did not fall within  
 211 any of the five categories were scored in a separate "Other" category (28%). Results for each of  
 212 these overdiagnosis contexts are discussed below.

213 *Table 2. Descriptions and examples of context of overdiagnosis discussion*

<b>Overdiagnosis context</b>	<b>Description</b>	<b>Example</b>	<b>Ref.</b>
Overdiagnosis estimation	Providing a quantitative estimate of overdiagnosis	<i>Estimation of overdiagnosis in low-dose computed tomography screening for lung cancer</i>	(28)
Disease definition	Setting thresholds to define the absence or presence of a disease, or distinguishing between two subcategories within a disease	<i>Current definitions of airflow obstruction and COPD yield overdiagnosis in primary care</i>	(29)
Overdiagnosis communication	Assessing and improving the understanding of overdiagnosis in the general public, and improving overdiagnosis dissemination by the healthcare professionals	<i>Assessing what the general public thinks is meant by the term 'overdiagnosis'</i>	(30)
Incidental findings	An abnormality found of an unrelated condition during either diagnostic testing or surgery	<i>Relevance of incidental findings when screening for a disorder in the abdominal area using multi-detector contrast-enhanced CT</i>	(31)
Genomics	Spurious genetic abnormalities	<i>Implications of genetic screening for common cancers in children</i>	(32)

## 215 *Overdiagnosis estimation*

216 The most common context of discussion relates to overdiagnosis estimation, accounting for  
 217 53% of all studies. These articles could be divided into two groups. The first were studies  
 218 attempting to estimate the degree of overdiagnosis in their respective clinical fields. (79%) These  
 219 often described the impact of implementation or a threshold shift of a diagnostic or screening  
 220 intervention on the rate of overdiagnosis. Notable examples of this are PSA testing for prostate  
 221 cancer and mammography for breast cancer. (33-38) However several articles estimated

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3 222 overdiagnosis in symptomatic conditions, such as incorrect diagnosis by untrained clinicians in  
4 223 patients presenting with malaria-like symptoms, leading to false-positives and unnecessary  
5 224 treatment. (26, 27) This should rather be considered misdiagnosis (incorrect diagnosis of a  
6 225 symptomatic person with a condition they do not have (1)) due to inaccuracy of clinical tests  
7 226 used in practice leading to false-positives, incorrect disease labels, and overtreatment. The  
8 227 second group represented studies that report methodological approaches for *how* one should  
9 228 estimate overdiagnosis. (21%) Differences regarding definitions used, measurement, study  
10 229 design and methods for estimation can lead to different results (39), hence there is often a large  
11 230 spread in these estimates, resulting in controversy regarding the true impact of overdiagnosis in  
12 231 the field.

### 13 232 *Disease definition*

14 233 In 15% of all studies disease definition was addressed. A relatively high proportion of these  
15 234 studies was addressed in the context of mental disorders (28%). Common topics included  
16 235 application of DSM for bipolar disorder, depression and ADHD, (40, 41) and physician diagnosis  
17 236 of COPD asthma, which were related to misdiagnosis rather than actual overdiagnosis. (42-  
18 237 44)The other major contributor was in oncology (25%), where the main issue was the transition  
19 238 of benign to malignant growths. Examples of such pre-disease conditions are DCIS, early stage  
20 239 prostate tumors and papillary thyroid carcinoma. (45-47)

### 21 240 *Overdiagnosis communication*

22 241 Communication about overdiagnosis with patients or the public accounted for 3% of all 1851  
23 242 publications. This mainly involved the people's understanding of the concept of overdiagnosis,  
24 243 and whether they perceived it to be an issue. (30, 48, 49) Other articles dealt with  
25 244 communication of overdiagnosis between the patient and the treating physician, (50, 51) or the  
26 245 development and effectiveness of decision aids. (52, 53)

### 27 246 *Other contexts*

28 247 Scientific literature on overdiagnosis in genomics and incidental findings were found only  
29 248 sporadically (0.4% and 0.8%). The term overmedicalisation was frequently used in literature to  
30 249 describe medicalisation of normal life events, such as birth, adolescence and death. Quaternary  
31 250 prevention was mostly used to describe the action being taken to prevent overmedicalisation.  
32 251 One of the most commonly observed topics in the other category was drivers and consequences  
33 252 of overdiagnosis. (18, 21, 54, 55) These were often mentioned alongside in narrative reviews on  
34 253 overdiagnosis. Furthermore, trend studies were common, describing the possibility of  
35 254 overdiagnosis based on a rapid increase in the number of diagnoses, without any significant  
36 255 decrease in the mortality rate. These studies did not provide an exact overdiagnosis estimate,  
37 256 but rather an indication that overdiagnosis might be occurring or increasing, based on historic

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3 257 data. Another context in which overdiagnosis was commonly addressed, especially in the last  
4 258 couple of years, was its definition. These studies aim at formulating accurate and appropriate  
5 259 definitions of overdiagnosis as well as related terminology (e.g. overmedicalisation,  
6 260 overdetection, disease mongering). In addition, some have attempted defining broad overall  
7 261 classifications to provide guidance for distinction between different overdiagnosis subtypes. (13,  
8 262 16)

## 13 263 **Discussion**

14  
15 264 This scoping review provides insight in the current landscape of overdiagnosis. There is great  
16 265 diversity in study characteristics across medical disciplines and in the contexts in which  
17 266 overdiagnosis is discussed. Some characteristics correlate with specific clinical fields, with, for  
18 267 example, screening occurring predominantly in oncological studies and medical examination  
19 268 being the most prevalently used diagnostic test for mental disorders.

20 269 Overdiagnosis is discussed in a variety of contexts, however three could be distinguished which  
21 270 invoked significant debate: 1) differences in overdiagnosis definition, 2) differences in methods  
22 271 used, leading to varying overdiagnosis estimates, and 3) typologies for overdiagnosis.

### 23 272 Overdiagnosis definitions

24 273 The definition of overdiagnosis has been topic of discussion for some time. In a narrow sense it  
25 274 refers to a diagnosis that does not result in a net benefit for an individual. (1) This can be viewed  
26 275 within an individual or on a group level, where benefits (early detection of clinically relevant  
27 276 disease) are weighted against the deficits (overdiagnosis and its associated consequences).  
28 277 However, not all studies follow this definition, but rather describe overdiagnosis as a diagnosis  
29 278 of a "disease" in an individual, that will never go on to cause symptoms or early death. (7) Using  
30 279 this definition, overdiagnosis in most mental disorders is impossible, as virtually all of these deal  
31 280 with symptomatic individuals, and do not typically lead to early death. Others have used the  
32 281 relation between pathology and symptoms as a measure of overdiagnosis. (56, 57) In the latter  
33 282 there is no doubt there is a clear abnormality, however it is uncertain whether smaller forms of  
34 283 this abnormality still significantly correlate with future clinically relevant disease. Ultimately, the  
35 284 question would be how or even if we should treat these individuals. These examples of  
36 285 definitions demonstrate the heterogeneity and complexity of the concept of overdiagnosis, and  
37 286 have led to the discussion regarding the extent or even the existence of overdiagnosis.

### 38 287 Methods for overdiagnosis estimation

39 288 Another discussion revolves around variation in estimates of overdiagnosis. Major trials such as  
40 289 the European Randomized Study of Screening for Prostate Cancer (ERSPC), the National Lung  
41 290 Screening Trial (NLST), the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial,

1  
2  
3 291 and the Malmö breast cancer screening trial, often form the basis for these discussions. (58-61)  
4  
5 292 These trials look into the effects of cancer screening programs. The ERSPC did not provide an  
6  
7 293 overdiagnosis in prostate cancer screening in their initial publication (62), but did provide an  
8  
9 294 estimate of 41% in their 2014 publication. (58) However, this was obtained through modelling,  
10  
11 295 and not calculated directly from the observed data. The NLST merely states that overdiagnosis is  
12  
13 296 presumably not large, as the number of breast cancers diagnosed between the two screening  
14  
15 297 arms is comparable. (59) And the PLCO and Malmö breast cancer screening trials did not state  
16  
17 298 anything about overdiagnosis. (60, 61) The scientific community reacted by using different  
18  
19 299 methods to provide overdiagnosis estimates for these trials. The rate of overdiagnosis that is  
20  
21 300 estimated depends on various features such as the definitions and measurements used, study  
22  
23 301 design and context and estimation approaches applied. (12, 39, 63-67) The latter can be divided  
24  
25 302 in lead-time (the time between screening detection and clinical presentation) and excess  
26  
27 303 incidence approach (excess number of cases between a screening and non-screening group),  
28  
29 304 each of which has its merits and issues, and requires assumptions to be made. Ultimately, the  
30  
31 305 variety in methodology used has resulted in variation in overdiagnosis estimates, and significant  
32  
33 306 controversy between studies. (11, 67, 68)

### 307 Overdiagnosis typologies

308 Several studies have provided overviews and acknowledged that finding a singular definition of  
309 overdiagnosis may not be feasible. However providing an overdiagnosis classification, aimed at  
310 describing subtypes of overdiagnosis, could prove to be useful. Some efforts have been made to  
311 create such a typology, however this is challenging as definitions vary widely and classifications  
312 can be made over different axes. Hence, this is a complex issue which should be addressed in a  
313 systematic manner. A comprehensive typology could aid researchers in their communication as  
314 was already suggested in a paper by Moynihan et al in 2012. (6) A recent paper by Rogers  
315 described the use of maldetection (issues with our understanding of what 'truly' disease is) and  
316 misclassification (an implicit or explicit threshold shift resulting in overdiagnosis). (13) Shortly  
317 after, Carter et al described the concepts of predatory, tragic and misdirected overdiagnosis. (17)  
318 Other work by Hofmann takes a more sociological and philosophical point of view. In his 2017  
319 publication, indicative, measurable and observable phenomena are used to describe the  
320 different stages in which a phenomenon develops into a clinical manifestation. (16) In oncology  
321 a tumor-patient classification has been described, relating to tumors that are regressive, non-  
322 progressive or truly malignant disease. (69) Although these works provide great improvement in  
323 our understanding of the issues at hand, they do not give further guidance as to how these  
324 concepts should be used in clinical research.

### 325 Strengths and limitations



1  
2  
3 326 To our knowledge, this is the first scoping review performed on the subject of overdiagnosis. It  
4  
5 327 provides broad insight in the available research on specific topics within overdiagnosis. To  
6  
7 328 appreciate the findings in this review, the following limitations should be considered. First,  
8  
9 329 studies were excluded when they did not have full text available. This may have led to exclusion  
10  
11 330 of a selection of relevant articles, but not a systematic exclusion of a particular range of  
12  
13 331 overdiagnosis studies. The same holds true for the lack of search criteria for iatrogenic disease,  
14  
15 332 overtreatment, and overutilisation. The issue in identifying studies discussing overdiagnosis, is  
16  
17 333 that there are no clear selection criteria to find these. Terminologies used to describe  
18  
19 334 overdiagnosis differ between studies, are widely spread and search filters in medical databases  
20  
21 335 are lacking. Hence, our goal was not to perform a comprehensive search. Instead, we aimed at  
22  
23 336 finding a large representative of papers discussing overdiagnosis.

24  
25 337 Second, unexpectedly, studies on genomics and incidental findings (or incidentalomas) were  
26  
27 338 largely missed. Forward reference checking revealed that some of the papers not found in our  
28  
29 339 search may use other terminology for describing overdiagnosis, such as the "prevalence of  
30  
31 340 significant findings" or "diagnostic value". Using our search strategy these articles were  
32  
33 341 unfortunately omitted and not included in this review. When researchers are interested  
34  
35 342 particularly in this subset, the information in this review might not suffice.

36  
37 343 In summary, overdiagnosis is a topic discussed over medical disciplines, and in a wide array of  
38  
39 344 contexts, from conceptual ideas in definition to practical issues for clinicians in daily practice.  
40  
41 345 The various characteristics of studies looking at overdiagnosis suggest that there may be  
42  
43 346 different (and sometimes multiple) underlying mechanisms through which it may manifest itself.  
44  
45 347 A lack of consensus on what is called overdiagnosis hampers communication between  
46  
47 348 researchers, physicians, patients, and policy makers. The use of overdiagnosis to describe  
48  
49 349 misdiagnosis will dilute its actual meaning, result in linguistic confusion, and counterproductive  
50  
51 350 discussion, and should thus be avoided. Providing clarity on the mechanisms that lead to  
52  
53 351 overdiagnosis will aid researchers communicate their results, especially with regard to  
54  
55 352 overdiagnosis estimates. Future methodological studies should focus on establishing a  
56  
57 353 framework to aid clinicians and researchers in understanding the different subtypes of  
58  
59 354 overdiagnosis, their consequences, and provide guidance for selecting appropriate study  
60  
355 designs and methods that match the research question of interest.

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17  
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26  
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31 380 *KGMM, LH and CAN all have approved the final version to be published, and its accuracy and integrity.*

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34 381 **Data sharing statement**

35  
36 382 *Readers interested in utilizing our database on overdiagnosis for specific purposes related to their respective*  
37 383 *research are invited to do so by contacting the first author through the corresponding email address.*

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**Additional information Figure 1**

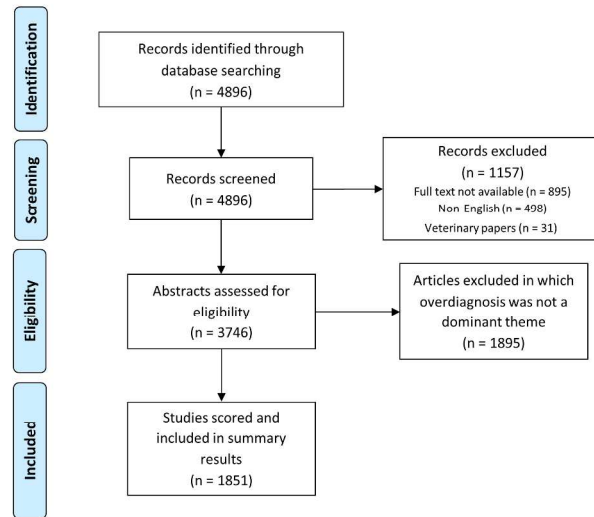
Caption: Flow-diagram of article selection for further review and scoring

Insertion: Line 170

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Flow-diagram of article selection for further review and scoring

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Criteria for scoring (title and abstract)		
Criterion	Outcome	Description
Full-text available	Yes / No	Is a full-text available from pubmed?
Veterinary study	Yes / No	Is the paper a study with animals?
Overdiagnosis as a dominant theme	Yes / No	Is overdiagnosis discussed as a specific dominant theme <b>Include:</b> Prognostic / prediction studies relating to disease progression <b>Include:</b> Trend studies. Index test will often be not addressed <b>Include:</b> Active surveillance studies that assess what the impact is of having a in-between category, next to treat and do not treat <b>Exclude:</b> Studies in which no diagnostic method is evaluated <b>Exclude:</b> Erratums <b>Exclude:</b> Case-studies (n = < 10) <b>Exclude:</b> Overview articles without a specific focus on diagnostics <b>Exclude:</b> Articles not mentioning overdiagnosis or only briefly commenting on it (particularly in the discussion) Example: Exclude article which states: "When Diagnostic test X is replaced with Diagnostic test Y sensitivity and specificity may be improved. As a result overdiagnosis of Disease Z may be reduced"
Clinical field	Bone & connective tissue	Examples: Myopathy, osteoporosis, dental problems
	Cancer	Examples: Prostate cancer, breast cancer, leukemia <b>Exclude:</b> cervical cancer caused by HPV (=infection)
	Cardiovascular	Examples: Pulmonary embolism, angina
	Congenital	Examples: Down syndrome, hypospadias
	Ear	Example: Tinnitus
	Eye	Example: Juncgevitis
	Gastrointestinal	Examples: Crohn's disease, reflux disease, liver failure
	Gynaecology & Obstetrics	Example: Preeclampsia
	Immune system	Examples: Allergic reactions, autoimmune disorders, Heparin induced thrombocytopenia (HIT), PANDA's, Rheumatoid arthritis
	Infection	Examples: Malaria, HIV, HPV, Clostridium difficile, pneumonia
	Mental	Examples: ADHD, autism, depression, schizophrenia, bipolar disorder, (vascular) dementia <b>Include:</b> Diseases that are primarily psychiatric disorders and often result in impaired cognitive function <b>Exclude:</b> See neurological disorders
	Metabolic	Examples: Diabetes, hypogonadism, hypothyroidism, growth related 'disorders', nutrition status
	Neurological	Example: Multiple sclerosis, Parkinsons, Alzheimer <b>Include:</b> Diseases of the central / periphial nervous systema, that often have motorical implications <b>Exclude:</b> See mental disorders
	Perinatal	Example: Malnutrition of the unborn child, child specific problems during pregnancy <b>Include:</b> disease in the unborn child
Respiratory	Examples: COPD, asthma, nasal disorders	
Skin	Example: Eczema	
Trauma	Examples: Car accidents, cuts, fractures, sprains, injury during surgery	
Urogenital	Examples: Chronic kidney failure, kidney stones	
No specific clinical field	Multiple clinical domains are assessed <b>OR</b> it is unclear if the paper focusses on a specific clinical domains Example: a methodological paper on how we should quantify overdiagnosis	
Study aim	Methodological	Papers desribing a theoretical framework for assessing overdiagnosis <b>Include:</b> Commentaries discussing the way overdiagnosis was determined in a different empirical primary study <b>Include:</b> Combination papers; Papers that are empirical, but also have a strong methodological focus on overdiagnosis <b>Include:</b> Modelling studies
	Non-methodological	Results from a primary study or assessment of outcomes by a review / overview paper
Article type	Commentary	A comment, reply or rebuttal on a previously published paper or commentary
	Narrative review	A paper giving a broad oversight of a specific topic, often from one particular authors view <b>Include:</b> editorials <b>Include:</b> opinion pieces <b>Include:</b> interviews <b>Include:</b> guidelines <b>Exclude:</b> Overviews that only refer to 1 or 2 accuracy studies, without further discussion on the topic of overdiagnosis
	Primary paper	Consists of a collection of original primary data collected by the researcher
	Systematic review	Collection and synthesis of available evidence on a topic. <b>Include:</b> Systematic assessments / meta-analyses of various articles within a specific domain <b>Exclude:</b> General discussions and exposes about a subject without a clear structural approach
Type of diagnostic test	Biomarker	Any measurement of chemicals in the human body as well as genotyping <b>Include:</b> immunohistochemistry (even though this may be assessed via microscopy in some cases) <b>Include:</b> Rapid diagnostic test for malaria
	Histology	Qualitative visual assessment of a target tissue through biopsy under a microscope (or similar devices) <b>Exclude:</b> Rapid diagnostic test for malaria (biomarker) <b>Exclude:</b> Scopy's (medical examination)
	Imaging	Any form of digital visualisation of the human body, such as MRI, CT, EKG, EEG, etc <b>Exclude:</b> Scopy's (medical examination)
	Medical examination	(Quick) medical tests that are performed directly by the clinician, either with or without specific medical equipment <b>Include:</b> Endoscopy, coloscopy, spirometry, reflex test, exploratory surgery, DSM-V assessment, psychological evaluations, skin prick tests (for allergy), blood pressure measurement <b>Include:</b> Assessment of medical history of the patient by a clinician, such as age, gender, smoking habits, exercise pattern, etc
	Prediction model	List of predictors used in a prediction model <b>Exclude:</b> Overall assessments using multiple tests (= "none") <b>Exclude:</b> Modelling studies that evaluate one particular index test, while using input on transition predictions in the rest of that model <b>Note:</b> Other index tests can not be checked with a prediction model, since they will be part of that model
	None	Not one specific test is studied (so a broad range of tests or no specific one is addressed) <b>Include:</b> Overview papers that only discuss the general topic of overdiagnosis <b>Include:</b> Papers discussing various tests (hence there is no specific index test)

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3	Screening	Yes / No
4		Is the primary focus of the study on diagnosis or detection in asymptomatic patients? <b>Include:</b> Screening is mentioned multiple times and explicitly <b>Exclude:</b> Screening as an example in an overview / review paper <b>Exclude:</b> Prognostic studies in patients that already received diagnosis
5	Overdiagnosis context	Overdiagnosis estimation
6		Overdiagnosis relating to the effect that a diagnostic test has on the number of excess cases found <b>Include:</b> Overdiagnosis mentioned in the results <b>Include:</b> Accuracy studies quantifying false-positive findings or % of overdiagnosis <b>Include:</b> Modelling papers that quantify overdiagnosis <b>Exclude:</b> Comparison of two diagnostic tests, without <b>explicit</b> quantification / assessment of overdiagnosis <b>Exclude:</b> Misdiagnosis / misclassification (= disease definition) <b>Exclude:</b> Overview papers that only briefly mention results from other primary studies <b>Exclude:</b> Overview papers that mention some quantitative results of overdiagnosis, but predominantly have a more broad discussion in general (=other)
7		Disease definition
8		Overdiagnosis as a result of shifting the disease definition in terms of biomarker threshold or criteria in a scoring list <b>Include:</b> Misclassification / misdiagnosis <b>Include:</b> Papers assessing pathologic / biologic / mechanistic background of the disease in context with overdiagnosis. <i>However be critical whether these directly link particular biologic subclassifications of a disease to overdiagnosis</i>
9		Overdiagnosis communication
10		Overdiagnosis as subject of communication between clinicians and/or patients <b>Include:</b> Studies that assess overdiagnosis communication to patients before or after diagnostic tests <b>Include:</b> Studies assessing people's general understanding of the concept of overdiagnosis
11	Incidental findings	Overdiagnosis as a coincidental finding resulting from diagnostic testing of an unrelated illness
12	Genomics	Overdiagnosis resulting from genome (screening) assessments, determining high-risk groups
13	Other	Overdiagnosis that can not be related to any of the categories above <b>Include:</b> Overview paper describing multiple aspects of overdiagnosis (e.g. accuracy, definition, litigation, methodology) <b>Include:</b> Studies looking at the downstream consequences of overdiagnosis (e.g. quality of life) <b>Include:</b> Studies looking at overall reasons for clinicians to overdiagnose (e.g. litigation risk, carefullness, unaware of negative consequences) <b>Include:</b> Trend studies <b>Include:</b> Studies on drivers and consequences of overdiagnosis
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# BMJ Open

## Overdiagnosis across medical disciplines: a scoping review

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3 **1 Title**

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3 **Abstract**  
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6 **Objective** To provide insight into how and in what clinical fields overdiagnosis is studied, and  
7 give directions for further applied and methodological research.  
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10 **Design** Scoping review

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12 **Data sources** Medline up to August 2017

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14 **Study selection** All English studies on humans, in which overdiagnosis was discussed as a  
15 dominant theme.  
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18 **Data extraction** Studies were assessed on clinical field, study aim (i.e. methodological or non-  
19 methodological), article type (e.g. primary study, review), the type and role of diagnostic test(s)  
20 studied, and the context in which these studies discussed overdiagnosis.  
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23  
24 **Results** From 4896 studies, 1851 were included for analysis. Half of all studies on overdiagnosis  
25 were performed in the field of oncology (50%). Other prevalent clinical fields included mental  
26 disorders, infectious diseases and cardiovascular diseases accounting for 9%, 8% and 6% of  
27 studies respectively. Overdiagnosis was addressed from a methodological perspective in 20% of  
28 studies. Primary studies were the most common article type (58%). The type of diagnostic tests  
29 most commonly studied were imaging tests (32%), although these were predominantly seen in  
30 oncology and cardiovascular disease (84%). Diagnostic tests were studied in a screening setting  
31 in 43% of all studies, but as high as 75% of all oncological studies. The context in which studies  
32 addressed overdiagnosis related most frequently to its estimation, accounting for 53%.  
33 Methodology on overdiagnosis estimation and definition provided a source for extensive  
34 discussion. Other contexts of discussion included definition of disease, overdiagnosis  
35 communication, trends in increasing disease prevalence, drivers and consequences of  
36 overdiagnosis, incidental findings and genomics.

37  
38 **Conclusions** Overdiagnosis is discussed across virtually all clinical fields and in different  
39 contexts. The variability in characteristics between studies and lack of consensus on  
40 overdiagnosis definition indicate the need for a uniform typology to improve coherence and  
41 comparability of studies on overdiagnosis.  
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3 40 **Strengths and limitations of this study**  
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- 6 41 - First complete overview of overdiagnosis across medical disciplines  
7 42 - Identification of the dominant clinical fields in which overdiagnosis is being studied, what  
8 43 characteristics these papers have, and in what context it is being studied  
9 44 - Not a fully comprehensive systematic review, due to widespread variation in terminology  
10 45 and concepts used related to overdiagnosis  
11 46 - Studies on incidental findings were likely missed due to usage of different terminology  
12 47 to describe overdiagnosis  
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## 49 Introduction

50 Overmedicalisation is the broad overarching term describing the use of “too much medicine”. (1)  
51 It encompasses various concepts such as disease mongering, misdiagnosis, overutilization,  
52 overdiagnosis and overtreatment. Initiatives relating to these concepts have begun to flourish  
53 on a global scale under the ‘Choosing Wisely’ initiative and in national programs such as Slow  
54 Medicine (Italy, the Netherlands and Brazil), Quaternary Prevention (Belgium) and Do not do  
55 (UK). (2, 3) A subcategory of the aforementioned concepts is overdiagnosis. This has become an  
56 even more popular term especially over the last two decades. (4-9) Furthermore, an annual  
57 conference going by the name of “Preventing Overdiagnosis”, dedicated to issues surrounding  
58 this concept, has been gaining popularity ever since its start in 2013, demonstrating a growing  
59 interest in the topic. (10) In this scoping review we will focus specifically on overdiagnosis.

60 Defining overdiagnosis is challenging and diverse definitions exist. (11, 12) In a narrow sense,  
61 overdiagnosis describes individuals receiving a diagnosis with a condition that would never have  
62 become symptomatic before the end of the individual’s life. (5, 7) However, overdiagnosis has  
63 also been described as giving a diagnosis that would not yield a net benefit. (1) These  
64 definitions are not similar, and thus may lead to different interpretations of (the extent of)  
65 overdiagnosis. Consequently, the mechanisms leading to overdiagnosis may also differ. Labeling  
66 an individual with a blood pressure over a certain threshold as hypertensive, and thus  
67 “diseased”, is conceptually different than not knowing whether one should diagnose an  
68 individual with a very small potentially malignant growth as having cancer, and thus “diseased”.  
69 Providing definitions in combination with mechanisms of overdiagnosis for a typology is  
70 challenging and source of extensive discussion. (13-17)

71 The range of overdiagnosis drivers is also extensive. It, amongst others, includes technological  
72 developments that detect smaller abnormalities than ever before which might not become  
73 clinically manifest. Furthermore, the use of large scale screening programs, inappropriate  
74 application of diagnostic criteria, legal incentives, cultural beliefs (i.e. that we should do  
75 everything in our power to find and treat disease) and commercial or professional interests have  
76 driven overdiagnosis. (6, 18-20)

77 Consequences of overdiagnosis may be serious and can be subdivided in negative effects on  
78 patient health and additional costs within the health care system. (21) Health effects include  
79 impaired quality of life and early loss of life due to side-effects or complications of unnecessary  
80 subsequent testing or treatment. Incorrectly labeling of individuals as patients may also lead to  
81 stigmatization, impacting psychological well-being and indirectly exert social effects through  
82 eligibility for health benefits. In monetary terms, overdiagnosis can result in unwarranted usage  
83 of (follow-up) tests, treatment and healthcare facilities and services.

84 Despite the increasing number of publications on overdiagnosis, ranging from discussions on  
85 overdiagnosis definition to estimating its impact, a scoping analysis on overdiagnosis is still  
86 lacking. In the present study, we provide an overview of research that has been performed  
87 across medical disciplines surrounding the topic of overdiagnosis. Not only will we give insight  
88 into how and in what clinical fields overdiagnosis is studied, but also provide directions for  
89 further applied and methodological research to investigate the mechanisms and impact of  
90 overdiagnosis, and to generate directions for reducing or preventing overdiagnosis.

## 91 **Methods**

92 PubMed was searched on August 2017 for published articles using keywords related to  
93 overdiagnosis, overdetection, overscreening, insignificant disease, overtesting,  
94 overmedicalisation, pseudodisease, inconsequential disease, and quaternary prevention, by  
95 using the following query:

96 *overdiagnos\*[tw] OR over diagnos\*[tw] OR overdetect\*[tw] OR over detect\*[tw] OR "insignificant*  
97 *disease"[tw] OR overscreen\*[tw] OR over screen\*[tw] OR overtest\*[tw] OR over test\*[tw] OR*  
98 *overmedical\*[tw] OR over medical\*[tw]OR "pseudodisease"[tw] OR "pseudo disease"[tw] OR*  
99 *"inconsequential disease"[tw] OR "Quaternary prevention"[tw]*

100 These terms were chosen as they were believed to capture most concepts related to  
101 overdiagnosis, generating a representative set of articles. All English articles on humans where  
102 the full text was available were included. Articles in which overdiagnosis was a dominant theme  
103 were included. Overdiagnosis was considered a dominant theme when a paper clearly addressed  
104 overdiagnosis as an issue being investigated or discussed. For example, a study on the adoption  
105 of a new threshold guideline for PSA prostate cancer screening was considered to have a  
106 dominant overdiagnosis theme. In contrast, a study that used overdiagnosis as a buzzword and  
107 merely suggested in the discussion that overdiagnosis might possibly play a role or have  
108 occurred, was excluded. Studies with overdiagnosis as a dominant theme were included  
109 regardless of which definition of overdiagnosis the authors adopted.

110 The titles and abstracts of the included studies were then screened. Included studies were  
111 assessed using (a list of) prespecified criteria. These criteria were established by screening the  
112 first 200 studies of the search query. They included clinical field, study aim, article type, type of  
113 diagnostic test, whether this was a screening test, and the context in which overdiagnosis was  
114 discussed. These criteria are described below (see further details in the supplementary file).  
115 Articles were assessed based solely on title and abstract. If an abstract was unavailable (e.g.  
116 opinion pieces), the full text was scanned.

### 117 Clinical field



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3 118 The clinical field to which the study belonged was determined using the ICD-10 classification.  
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5 119 When a study addressed more than one clinical field or did not address overdiagnosis within a  
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7 120 specific clinical field, but discussed overdiagnosis on a more general level, they were included in  
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9 121 the separate category "No specific clinical field".

#### 10 122 Study aim

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12 123 Two study aims were distinguished: 1) studies focusing on *how* overdiagnosis should be studied.  
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14 124 These are studies with a methodological aim. Examples are studies looking into how  
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16 125 overdiagnosis estimations are affected by the methods used, or studies providing a framework  
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18 126 for the definition of overdiagnosis. Simulation studies using mathematical models for estimating  
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20 127 the extent of overdiagnosis were also classified as methodological studies. Studies not  
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22 128 addressing the aforementioned concepts, but rather provide, for example, a qualitative overview  
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24 129 of the (possible) impact of overdiagnosis in a certain field, or calculate overdiagnosis estimates  
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26 130 from empirical data, were considered to have 2) a non-methodological aim.

#### 27 131 Article type

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29 132 Studies were classified using four article types: primary studies, narrative reviews, systematic  
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31 133 reviews or commentaries. Primary studies used data collected from trials, observational studies  
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33 134 or generated using simulation models. Narrative reviews described a broad oversight on  
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35 135 overdiagnosis. These included editorials, opinion pieces, interviews and overviews. Systematic  
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37 136 reviews stated a specific hypothesis and tested this using a systematic approach to gather  
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39 137 existing literature. If a systematic approach was lacking, these studies were scored as narrative  
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41 138 reviews. Studies were considered commentaries when they, replied to previously published  
42  
43 139 papers.

#### 44 140 Type of diagnostic test

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46 141 Diagnostic tests were categorized into six types: imaging, medical examination, biomarker,  
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48 142 histology, prediction model or various. Whenever a study looked into a combination of two  
49  
50 143 tests, both types were scored. For example, an image guided biopsy would be scored as both an  
51  
52 144 imaging and histologic diagnostic test. If three or more diagnostic tests were addressed within a  
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54 145 study, or overdiagnosis was addressed in a general context without any diagnostic test in  
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56 146 particular, this was scored under "Various tests".

#### 57 147 Screening

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59 148 When studies focused on a test used for screening groups of asymptomatic individuals, this was  
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149 scored as a screening study. Studies that did not explicitly state that the diagnostic test was  
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studied in the context of screening, were scored as a non-screening.

### 151 Overdiagnosis context

152 To assess the context in which studies discussed overdiagnosis five categories were defined:  
153 estimating extent of overdiagnosis, disease definition, overdiagnosis communication, incidental  
154 findings, and genomics. The first category, estimating extent of overdiagnosis, relates to all  
155 articles giving a quantified estimate of overdiagnosis. Disease definition revolves around the  
156 setting of thresholds to define the absence or presence of a disease or to distinguish between  
157 two subcategories of a certain disease (e.g. progressive and non-progressive forms).  
158 Overdiagnosis communication relates to studies aimed at assessing and improving the  
159 understanding of overdiagnosis in the general public, and improving overdiagnosis  
160 dissemination by the healthcare professionals. Studies addressing abnormalities found of an  
161 unrelated condition during either diagnostic testing or surgery were scored as studies on  
162 incidental findings. Spurious findings on genome wide screening tests were scored in the  
163 overdiagnosis context of genomics.

## 164 **Results**

165 The PubMed search resulted in a total number of 4896 studies identified. After application of the  
166 inclusion criteria 3746 studies were assessed for eligibility on title and abstract. Studies in which  
167 overdiagnosis was a dominant theme yielded 1851 studies. (Figure 1). Table 1 provides a  
168 summarized view of the characteristics of the total number of studies, the four largest clinical  
169 fields, all other remaining clinical domains and studies not related to a specific clinical field.

170 *[insert Figure 1 approximately here]*

### 171 Clinical field

172 Papers on overdiagnosis were found in all clinical fields, but were mainly published within  
173 oncology (50%), in which breast (34%), prostate (24%) and lung cancer (14%) ranked as most  
174 prevalently studied. Other clinical fields addressing overdiagnosis included mental disorders  
175 (9%), infectious diseases (8%) and cardiovascular disease (6%). Within these fields, studies were  
176 predominantly looking into bipolar disorder, malaria and pulmonary embolism (PE), respectively.  
177 (22-27)

### 178 Study aim

179 Studies addressing methodological issues consisted of 20%. The majority of these studies were  
180 performed within the field of oncology. However, non-methodological studies were the most  
181 common study aim used across all clinical fields, accounting for 80% of the total number of  
182 articles. These notably included studies using empirical data to assess the occurrence or  
183 estimate overdiagnosis for a specific disease.

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3 184 Article type  
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6 185 Primary studies (58%) were the most common article type discussing overdiagnosis. Of all  
7 186 included studies narrative, systematic reviews and commentaries represented 24%, 9% and 9%  
8 187 respectively. From all studies that addressed a specific clinical field, the proportion of systematic  
9 188 reviews and commentaries was relatively high within oncology.  
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12 189 Type of diagnostic test  
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14 190 Imaging was the most often encountered diagnostic test, accounting for 32% of all studies.  
15 191 Biomarkers (15%), histology (13%) and medical examination (17%) were approximately equally  
16 192 often found. Prediction models were less common (3%). The proportion not related to one  
17 193 particular diagnostic test of interest was 21%. Distributions of diagnostic tests varied  
18 194 significantly depending on the clinical field. Imaging was most prevalent in oncology where it  
19 195 accounted for 48% of diagnostic tests, mostly related to breast (53%) and lung cancer screening  
20 196 (21%). Within the field of mental disorders medical examination was often seen in the form of  
21 197 application of the DSM (Diagnostic and Statistical Manual of Mental Disorders) as diagnostic  
22 198 tool. Biomarkers and histology were seen relatively more frequent as diagnostic tests for  
23 199 infectious diseases when compared to other clinical fields.  
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30 200 Screening  
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32 201 Diagnostic testing was studied in the context of screening in 43% of studies. There was however  
33 202 a skewed distribution between clinical fields. Within oncology, 75% of all studies were related to  
34 203 screening, whereas for mental disorders, infectious diseases and cardiovascular diseases this was  
35 204 15% or lower.  
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*Table 1. Characteristics of papers in which overdiagnosis was a dominant theme. Results are shown for the total number of articles, the four largest clinical fields and studies not addressing a specific clinical field*

	<b>Total</b> <b>(n =1851)</b>	<b>Oncological</b> <b>disorders</b> <b>(n = 920)</b>	<b>Mental</b> <b>disorders</b> <b>(n =171)</b>	<b>Infectious</b> <b>diseases</b> <b>(n = 143)</b>	<b>Cardiovascular</b> <b>disorders</b> <b>(n = 105)</b>	<b>Other clinical</b> <b>fields</b> <b>(n = 390)</b>	<b>No specific</b> <b>clinical field</b> <b>(n = 122)</b>
<b>Study aim</b>							
Methodological	<b>20%</b>	30%	11%	4%	10%	4%	34%
Non-methodological	<b>80%</b>	70%	89%	96%	90%	96%	66%
<b>Article type</b>							
Primary study	<b>58%</b>	55%	53%	85%	61%	69%	27%
Narrative review	<b>24%</b>	22%	32%	9%	24%	22%	52%
Systematic review	<b>9%</b>	12%	8%	1%	10%	5%	11%
Commentary	<b>9%</b>	11%	8%	6%	6%	4%	10%
<b>Diagnostic test</b>							
Imaging	<b>32%</b>	48%	3%	4%	47%	19%	7%
Medical examination	<b>17%</b>	3%	58%	26%	26%	30%	4%
Biomarker	<b>15%</b>	16%	3%	29%	10%	16%	3%
Histology	<b>13%</b>	17%	0%	21%	2%	11%	2%
Prediction model	<b>3%</b>	4%	1%	2%	3%	4%	1%
Various	<b>21%</b>	13%	35%	18%	12%	20%	84%
<b>Screening</b>							
Yes	<b>43%</b>	75%	5%	10%	15%	10%	20%
No	<b>57%</b>	25%	95%	90%	85%	90%	80%
<b>Overdiagnosis context</b>							
Overdiagnosis estimation	<b>53%</b>	57%	22%	63%	65%	60%	16%
Disease definition	<b>15%</b>	8%	46%	13%	14%	22%	8%
Overdiagnosis communication	<b>3%</b>	5%	2%	0.7%	0%	0.8%	3%
Incidental findings	<b>0.8%</b>	0.8%	0%	0%	1%	1%	2%
Genomics	<b>0.4%</b>	0.3%	0%	0%	1%	0%	3%
Other*	<b>28%</b>	29%	30%	24%	19%	16%	67%

\*Subcategories in this category include: overdiagnosis definition, drivers and consequences of overdiagnosis and trend studies suggesting overdiagnosis

## 205 Overdiagnosis context

206 The context in which overdiagnosis was most frequently discussed related to its estimation  
 207 (53%). Only within the field of mental disorders was disease definition more frequently discussed  
 208 than overdiagnosis estimation (46% vs 22%). Descriptions and example studies on each of the  
 209 five predefined categories can be found in table 2. The majority of studies discussing  
 210 overdiagnosis (72%) were classifiable in one of these categories. Studies that did not fall within  
 211 any of the five categories were scored in a separate "Other" category (28%). Results for each of  
 212 these overdiagnosis contexts are discussed below.

213 *Table 2. Descriptions and examples of context of overdiagnosis discussion*

<b>Overdiagnosis context</b>	<b>Description</b>	<b>Example</b>	<b>Ref.</b>
Overdiagnosis estimation	Providing a quantitative estimate of overdiagnosis	<i>Estimation of overdiagnosis in low-dose computed tomography screening for lung cancer</i>	(28)
Disease definition	Setting thresholds to define the absence or presence of a disease, or distinguishing between two subcategories within a disease	<i>Current definitions of airflow obstruction and COPD yield overdiagnosis in primary care</i>	(29)
Overdiagnosis communication	Assessing and improving the understanding of overdiagnosis in the general public, and improving overdiagnosis dissemination by the healthcare professionals	<i>Assessing what the general public thinks is meant by the term 'overdiagnosis'</i>	(30)
Incidental findings	An abnormality found of an unrelated condition during either diagnostic testing or surgery	<i>Relevance of incidental findings when screening for a disorder in the abdominal area using multi-detector contrast-enhanced CT</i>	(31)
Genomics	Spurious genetic abnormalities	<i>Implications of genetic screening for common cancers in children</i>	(32)

## 215 *Overdiagnosis estimation*

216 The most common context of discussion relates to overdiagnosis estimation, accounting for  
 217 53% of all studies. These articles could be divided into two groups. The first were studies  
 218 attempting to estimate the degree of overdiagnosis in their respective clinical fields. (79%) These  
 219 often described the impact of implementation or a threshold shift of a diagnostic or screening  
 220 intervention on the rate of overdiagnosis. Notable examples of this are PSA testing for prostate  
 221 cancer and mammography for breast cancer. (33-38) However several articles estimated

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3 222 overdiagnosis in symptomatic conditions, such as incorrect diagnosis by untrained clinicians in  
4 223 patients presenting with malaria-like symptoms, leading to false-positives and unnecessary  
5 224 treatment. (26, 27) This should rather be considered misdiagnosis (incorrect diagnosis of a  
6 225 symptomatic person with a condition they do not have (1)) due to inaccuracy of clinical tests  
7 226 used in practice leading to false-positives, incorrect disease labels, and overtreatment. The  
8 227 second group represented studies that report methodological approaches for *how* one should  
9 228 estimate overdiagnosis. (21%) Differences regarding definitions used, measurement, study  
10 229 design and methods for estimation can lead to different results (39), hence there is often a large  
11 230 spread in these estimates, resulting in controversy regarding the true impact of overdiagnosis in  
12 231 the field.

### 13 232 *Disease definition*

14 233 In 15% of all studies disease definition was addressed. A relatively high proportion of these  
15 234 studies was addressed in the context of mental disorders (28%). Common topics included  
16 235 application of DSM for bipolar disorder, depression and ADHD, (40, 41) and physician diagnosis  
17 236 of COPD asthma, which were related to misdiagnosis rather than actual overdiagnosis. (42-44)  
18 237 The other major contributor was in oncology (25%), where the main issue was the transition of  
19 238 benign to malignant growths. Examples of such pre-disease conditions are DCIS, early stage  
20 239 prostate tumors and papillary thyroid carcinoma. (45-47)

### 21 240 *Overdiagnosis communication*

22 241 Communication about overdiagnosis with patients or the public accounted for 3% of all 1851  
23 242 publications. This mainly involved the people's understanding of the concept of overdiagnosis,  
24 243 and whether they perceived it to be an issue. (30, 48, 49) Other articles dealt with  
25 244 communication of overdiagnosis between the patient and the treating physician, (50, 51) or the  
26 245 development and effectiveness of decision aids. (52, 53)

### 27 246 *Other contexts*

28 247 Scientific literature on overdiagnosis in genomics and incidental findings were found only  
29 248 sporadically (0.4% and 0.8%). The term overmedicalisation was frequently used in literature to  
30 249 describe medicalisation of normal life events, such as birth, adolescence and death. Quaternary  
31 250 prevention was mostly used to describe the action being taken to prevent overmedicalisation.  
32 251 One of the most commonly observed topics in the other category was drivers and consequences  
33 252 of overdiagnosis. (18, 21, 54, 55) These were often mentioned alongside in narrative reviews on  
34 253 overdiagnosis. Furthermore, trend studies were common, describing the possibility of  
35 254 overdiagnosis based on a rapid increase in the number of diagnoses, without any significant  
36 255 decrease in the mortality rate. These studies did not provide an exact overdiagnosis estimate,  
37 256 but rather an indication that overdiagnosis might be occurring or increasing, based on historic

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3 257 data. Another context in which overdiagnosis was commonly addressed, especially in the last  
4 258 couple of years, was its definition. These studies aim at formulating accurate and appropriate  
5 259 definitions of overdiagnosis as well as related terminology (e.g. overmedicalisation,  
6 260 overdetection, disease mongering). In addition, some have attempted defining broad overall  
7 261 classifications to provide guidance for distinction between different overdiagnosis subtypes. (13,  
8 262 16)

## 13 263 **Discussion**

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15 264 This scoping review provides insight in the current landscape of overdiagnosis. There is great  
16 265 diversity in study characteristics across medical disciplines and in the contexts in which  
17 266 overdiagnosis is discussed. Some characteristics correlate with specific clinical fields, with, for  
18 267 example, screening occurring predominantly in oncological studies and medical examination  
19 268 being the most prevalently used diagnostic test for mental disorders.

20 269 Overdiagnosis is discussed in a variety of contexts, however three could be distinguished which  
21 270 invoked significant debate: 1) differences in overdiagnosis definition, 2) differences in methods  
22 271 used, leading to varying overdiagnosis estimates, and 3) typologies for overdiagnosis.

### 23 272 Overdiagnosis definitions

24 273 The definition of overdiagnosis has been topic of discussion for some time. In a narrow sense it  
25 274 refers to a diagnosis that does not result in a net benefit for an individual. (1) This can be viewed  
26 275 within an individual or on a group level, where benefits (early detection of clinically relevant  
27 276 disease) are weighted against the deficits (overdiagnosis and its associated consequences).  
28 277 However, not all included studies give a clear definition, but implicitly use the definition of  
29 278 overdiagnosis as a diagnosis of a "disease" in an asymptomatic individual, that will never go on  
30 279 to cause symptoms or early death. (7) This definition is particular to the screening-context, but  
31 280 does not apply to a large portion of the studies found in this review that are on testing  
32 281 symptomatic individuals, for example those with mental disorders. Others have used the relation  
33 282 between pathology and symptoms as a measure of overdiagnosis. (56, 57) In the latter there is  
34 283 no doubt there is a clear abnormality, however it is uncertain whether smaller forms of this  
35 284 abnormality still significantly correlate with future clinically relevant disease. Ultimately, the  
36 285 question would be how or even if we should treat these individuals. These examples of  
37 286 definitions demonstrate the heterogeneity and complexity of the concept of overdiagnosis, and  
38 287 have led to the discussion regarding the extent or even the existence of overdiagnosis. Which  
39 288 definition researchers use for overdiagnosis needs to be reported completely to be able to  
40 289 judge the applicability of the results.

### 41 290 Methods for overdiagnosis estimation

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3 291 Another discussion revolves around variation in estimates of overdiagnosis. Major trials such as  
4 292 the European Randomized Study of Screening for Prostate Cancer (ERSPC), the National Lung  
5 293 Screening Trial (NLST), the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial,  
6 294 and the Malmö breast cancer screening trial, often form the basis for these discussions. (58-61)  
7 295 These trials look into the effects of cancer screening programs. The ERSPC did not provide an  
8 296 overdiagnosis in prostate cancer screening in their initial publication (62), but did provide an  
9 297 estimate of 41% in their 2014 publication. (58) However, this was obtained through modelling,  
10 298 and not calculated directly from the observed data. The NLST merely states that overdiagnosis is  
11 299 presumably not large, as the number of breast cancers diagnosed between the two screening  
12 300 arms is comparable. (59) And the PLCO and Malmö breast cancer screening trials did not state  
13 301 anything about overdiagnosis. (60, 61) The scientific community reacted by using different  
14 302 methods to provide overdiagnosis estimates for these trials. The rate of overdiagnosis that is  
15 303 estimated depends on various features such as the definitions and measurements used, study  
16 304 design and context and estimation approaches applied. (12, 39, 63-67) The latter can be divided  
17 305 in lead-time (the time between screening detection and clinical presentation) and excess  
18 306 incidence approach (excess number of cases between a screening and non-screening group),  
19 307 each of which has its merits and issues, and requires assumptions to be made. Ultimately, the  
20 308 variety in methodology used has resulted in variation in overdiagnosis estimates, and significant  
21 309 controversy between studies. (11, 67, 68)

### 310 Overdiagnosis typologies

311 Several studies have provided overviews and acknowledged that finding a singular definition of  
312 overdiagnosis may not be feasible. However providing an overdiagnosis classification, aimed at  
313 describing subtypes of overdiagnosis, could prove to be useful. Some efforts have been made to  
314 create such a typology, however this is challenging as definitions vary widely and classifications  
315 can be made over different axes. Hence, this is a complex issue which should be addressed in a  
316 systematic manner. A comprehensive typology could aid researchers in their communication as  
317 was already suggested in a paper by Moynihan et al in 2012. (6) A recent paper by Rogers  
318 described the use of maldetection (issues with our understanding of what 'truly' disease is) and  
319 misclassification (an implicit or explicit threshold shift resulting in overdiagnosis). (13) Shortly  
320 after, Carter et al described the concepts of predatory, tragic and misdirected overdiagnosis. (17)  
321 Other work by Hofmann takes a more sociological and philosophical point of view. In his 2017  
322 publication, indicative, measurable and observable phenomena are used to describe the  
323 different stages in which a phenomenon develops into a clinical manifestation. (16) In oncology  
324 a tumor-patient classification has been described, relating to tumors that are regressive, non-  
325 progressive or truly malignant disease. (69) Although these works provide great improvement in  
326 our understanding of the issues at hand, they do not give further guidance as to how these  
327 concepts should be used in clinical research.



## 328 Strengths and limitations

329 To our knowledge, this is the first scoping review performed on the subject of overdiagnosis. It  
330 provides broad insight in the available research on specific topics within overdiagnosis. To  
331 appreciate the findings in this review, the following limitations should be considered. First,  
332 studies were excluded when they did not have full text available. This may have led to exclusion  
333 of a selection of relevant articles, but not a systematic exclusion of a particular range of  
334 overdiagnosis studies. The same holds true for the lack of search criteria for iatrogenic disease,  
335 overtreatment, and overutilisation. The issue in identifying studies discussing overdiagnosis, is  
336 that there are no clear selection criteria to find these. Terminologies used to describe  
337 overdiagnosis differ between studies, are widely spread and search filters in medical databases  
338 are lacking. Hence, our goal was not to perform a comprehensive search. Instead, we aimed at  
339 finding a large representative of papers discussing overdiagnosis.

340 Second, unexpectedly, studies on genomics and incidental findings (or incidentalomas) were  
341 largely missed. Forward reference checking revealed that some of the papers not found in our  
342 search may use other terminology for describing overdiagnosis, such as the "prevalence of  
343 significant findings" or "diagnostic value". Using our search strategy these articles were  
344 unfortunately omitted and not included in this review. When researchers are interested  
345 particularly in this subset, the information in this review might not suffice.

346 In summary, overdiagnosis is a topic discussed over medical disciplines, and in a wide array of  
347 contexts, from conceptual ideas in definition to practical issues for clinicians in daily practice.  
348 The various characteristics of studies looking at overdiagnosis suggest that there may be  
349 different (and sometimes multiple) underlying mechanisms through which it may manifest itself.  
350 A lack of consensus on what is called overdiagnosis hampers communication between  
351 researchers, physicians, patients, and policy makers. The use of overdiagnosis to describe  
352 misdiagnosis will dilute its actual meaning, result in linguistic confusion, and counterproductive  
353 discussion, and should thus be avoided. Providing clarity on the mechanisms that lead to  
354 overdiagnosis will aid researchers communicate their results, especially with regard to  
355 overdiagnosis estimates. Future methodological studies should focus on establishing a  
356 framework to aid clinicians and researchers in understanding the different subtypes of  
357 overdiagnosis, their consequences, and provide guidance for selecting appropriate study  
358 designs and methods that match the research question of interest.

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35 384 **Data sharing statement**

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37 385 *Readers interested in utilizing our database on overdiagnosis for specific purposes related to their respective*  
38 386 *research are invited to do so by contacting the first author through the corresponding email address.*

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**Additional information Figure 1**

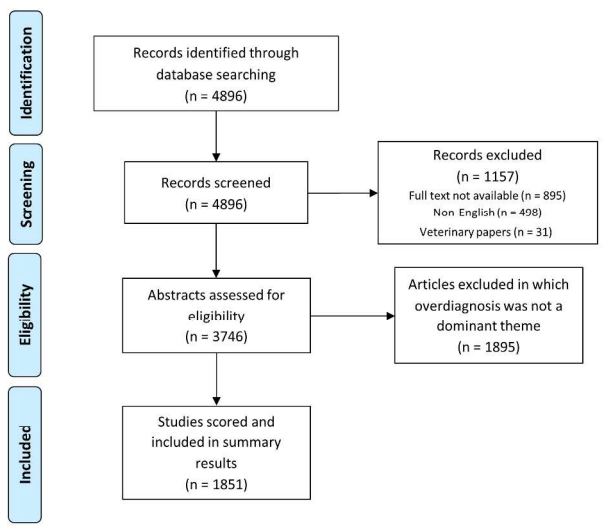
Caption: Flow-diagram of article selection for further review and scoring

Insertion: Line 170

Legend: - (this figure does not require a legend)

For peer review only

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Flow-diagram of article selection for further review and scoring

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Criteria for scoring (title and abstract)		
Criterion	Outcome	Description
Full-text available	Yes / No	Is a full-text available from pubmed?
Veterinary study	Yes / No	Is the paper a study with animals?
Overdiagnosis as a dominant theme	Yes / No	Is overdiagnosis discussed as a specific dominant theme <b>Include:</b> Prognostic / prediction studies relating to disease progression <b>Include:</b> Trend studies. Index test will often be not addressed <b>Include:</b> Active surveillance studies that assess what the impact is of having a in-between category, next to treat and do not treat <b>Exclude:</b> Studies in which no diagnostic method is evaluated <b>Exclude:</b> Erratums <b>Exclude:</b> Case-studies (n = < 10) <b>Exclude:</b> Overview articles without a specific focus on diagnostics <b>Exclude:</b> Articles not mentioning overdiagnosis or only briefly commenting on it (particularly in the discussion) Example: Exclude article which states: "When Diagnostic test X is replaced with Diagnostic test Y sensitivity and specificity may be improved. As a result overdiagnosis of Disease Z may be reduced"
Clinical field	Bone & connective tissue	Examples: Myopathy, osteoporosis, dental problems
	Cancer	Examples: Prostate cancer, breast cancer, leukemia <b>Exclude:</b> cervical cancer caused by HPV (=infection)
	Cardiovascular	Examples: Pulmonary embolism, angina
	Congenital	Examples: Down syndrome, hypospadias
	Ear	Example: Tinnitus
	Eye	Example: Juncgevitis
	Gastrointestinal	Examples: Crohn's disease, reflux disease, liver failure
	Gynaecology & Obstetrics	Example: Preeclampsia
	Immune system	Examples: Allergic reactions, autoimmune disorders, Heparin induced thrombocytopenia (HIT), PANDA's, Rheumatoid arthritis
	Infection	Examples: Malaria, HIV, HPV, Clostridium difficile, pneumonia
	Mental	Examples: ADHD, autism, depression, schizophrenia, bipolar disorder, (vascular) dementia <b>Include:</b> Diseases that are primarily psychiatric disorders and often result in impaired cognitive function <b>Exclude:</b> See neurological disorders
	Metabolic	Examples: Diabetes, hypogonadism, hypothyroidism, growth related 'disorders', nutrition status
	Neurological	Example: Multiple sclerosis, Parkinsons, Alzheimer <b>Include:</b> Diseases of the central / periphial nervous systema, that often have motorical implications <b>Exclude:</b> See mental disorders
	Perinatal	Example: Malnutrition of the unborn child, child specific problems during pregnancy <b>Include:</b> disease in the unborn child
Respiratory	Examples: COPD, asthma, nasal disorders	
Skin	Example: Eczema	
Trauma	Examples: Car accidents, cuts, fractures, sprains, injury during surgery	
Urogenital	Examples: Chronic kidney failure, kidney stones	
No specific clinical field	Multiple clinical domains are assessed <b>OR</b> it is unclear if the paper focusses on a specific clinical domains Example: a methodological paper on how we should quantify overdiagnosis	
Study aim	Methodological	Papers desribing a theoretical framework for assessing overdiagnosis <b>Include:</b> Commentaries discussing the way overdiagnosis was determined in a different empirical primary study <b>Include:</b> Combination papers; Papers that are empirical, but also have a strong methodological focus on overdiagnosis <b>Include:</b> Modelling studies
	Non-methodological	Results from a primary study or assessment of outcomes by a review / overview paper
Article type	Commentary	A comment, reply or rebuttal on a previously published paper or commentary
	Narrative review	A paper giving a broad oversight of a specific topic, often from one particular authors view <b>Include:</b> editorials <b>Include:</b> opinion pieces <b>Include:</b> interviews <b>Include:</b> guidelines <b>Exclude:</b> Overviews that only refer to 1 or 2 accuracy studies, without further discussion on the topic of overdiagnosis
	Primary paper	Consists of a collection of original primary data collected by the researcher
	Systematic review	Collection and synthesis of available evidence on a topic. <b>Include:</b> Systematic assessments / meta-analyses of various articles within a specific domain <b>Exclude:</b> General discussions and exposes about a subject without a clear structural approach
Type of diagnostic test	Biomarker	Any measurement of chemicals in the human body as well as genotyping <b>Include:</b> immunohistochemistry (even though this may be assessed via microscopy in some cases) <b>Include:</b> Rapid diagnostic test for malaria
	Histology	Qualitative visual assessment of a target tissue through biopsy under a microscope (or similar devices) <b>Exclude:</b> Rapid diagnostic test for malaria (biomarker) <b>Exclude:</b> Scopy's (medical examination)
	Imaging	Any form of digital visualisation of the human body, such as MRI, CT, EKG, EEG, etc <b>Exclude:</b> Scopy's (medical examination)
	Medical examination	(Quick) medical tests that are performed directly by the clinician, either with or without specific medical equipment <b>Include:</b> Endoscopy, coloscopy, spirometry, reflex test, exploratory surgery, DSM-V assessment, psychological evaluations, skin prick tests (for allergy), blood pressure measurement <b>Include:</b> Assessment of medical history of the patient by a clinician, such as age, gender, smoking habits, exercise pattern, etc
	Prediction model	List of predictors used in a prediction model <b>Exclude:</b> Overall assessments using multiple tests (= "none") <b>Exclude:</b> Modelling studies that evaluate one particular index test, while using input on transition predictions in the rest of that model <b>Note:</b> Other index tests can not be checked with a prediction model, since they will be part of that model
	None	Not one specific test is studied (so a broad range of tests or no specific one is addressed) <b>Include:</b> Overview papers that only discuss the general topic of overdiagnosis <b>Include:</b> Papers discussing various tests (hence there is no specific index test)

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3	Screening	Yes / No
4		<p>Is the primary focus of the study on diagnosis or detection in asymptomatic patients?</p> <p><b>Include:</b> Screening is mentioned multiple times and explicitly</p> <p><b>Exclude:</b> Screening as an example in an overview / review paper</p> <p><b>Exclude:</b> Prognostic studies in patients that already received diagnosis</p>
5	Overdiagnosis context	Overdiagnosis estimation
6		<p>Overdiagnosis relating to the effect that a diagnostic test has on the number of excess cases found</p> <p><b>Include:</b> Overdiagnosis mentioned in the results</p> <p><b>Include:</b> Accuracy studies quantifying false-positive findings or % of overdiagnosis</p> <p><b>Include:</b> Modelling papers that quantify overdiagnosis</p> <p><b>Exclude:</b> Comparison of two diagnostic tests, without <b>explicit</b> quantification / assessment of overdiagnosis</p> <p><b>Exclude:</b> Misdiagnosis / misclassification (= disease definition)</p> <p><b>Exclude:</b> Overview papers that only briefly mention results from other primary studies</p> <p><b>Exclude:</b> Overview papers that mention some quantitative results of overdiagnosis, but predominantly have a more broad discussion in general (=other)</p>
7		Disease definition
8		<p>Overdiagnosis as a result of shifting the disease definition in terms of biomarker threshold or criteria in a scoring list</p> <p><b>Include:</b> Misclassification / misdiagnosis</p> <p><b>Include:</b> Papers assessing pathologic / biologic / mechanistic background of the disease in context with overdiagnosis. <i>However be critical whether these directly link particular biologic subclassifications of a disease to overdiagnosis</i></p>
9		Overdiagnosis communication
10		<p>Overdiagnosis as subject of communication between clinicians and/or patients</p> <p><b>Include:</b> Studies that assess overdiagnosis communication to patients before or after diagnostic tests</p> <p><b>Include:</b> Studies assessing people's general understanding of the concept of overdiagnosis</p>
11	Incidental findings	Overdiagnosis as a coincidental finding resulting from diagnostic testing of an unrelated illness
12	Genomics	Overdiagnosis resulting from genome (screening) assessments, determining high-risk groups
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