Time arrow in published clinical studies/trials indexed in MEDLINE: a systematic analysis of Retrospective vs Prospective study design, from 1960 to 2017.

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Clinical studies/trials are experiments or observations on human subjects considered by the scientific community the most appropriate instrument to answer specific research questions on interventions on health outcomes. The time-line of the observations might be focused on a single time point or to follow time, backward or forward, in the so called, respectively, retrospective and prospective study design. Since the retrospective approach has been criticized for the possible sources of errors due to bias and confounding, we aimed this study to assess if there is a prevalence of retrospective vs prospective design in the clinical studies/trials by querying MEDLINE. Our results on a sample of 1,438,872 studies/trials, (yrs 1960-2017), support a prevalence of retrospective, respectively 55% vs 45%. To explain this result, arandom sub-sample of studies where the country of origin was reported (n=1576) was categorized in high and low-income based onthe nominal Gross Domestic Product (GDP) and matched with the topic of the research. As expected, the absolute majority of studies/trials are carried on by high-income countries, respectively 86% vs 14%; even if a slight prevalence of retrospective was recorded in both income groups, nonetheless the most part of prospective studies are carried out by high-GDP countries, 85% vs 15%. Finally the differences in the design of the study are understandable when considering the topic of the research.

1 **Time arrow in published clinical studies/trials indexed in MEDLINE: a systematic analysis**

2 **of retrospective vs prospective study design, from 1960 to 2017.**

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Abstract 250

Clinical studies/trials are experiments or observations on human subjects considered by the scientific community the most appropriate instrument to answer specific research questions on interventions on health outcomes. The time-line of the observations might be focused on a single time point or to follow time, backward or forward, in the so called, respectively, retrospective and prospective study design. Since the retrospective approach has been criticized for the possible sources of errors due to bias and confounding, we aimed this study to assess if there is a prevalence of retrospective vs prospective design in the clinical studies/trials by querying MEDLINE. Our results on a sample of 1,438,872 studies/trials, (yrs 1960-2017), support a prevalence of retrospective, respectively 55% vs 45%. To explain this result, a random sub-sample of studies where the country of origin was reported (n=1576) was categorized in high and low-income based on the nominal Gross Domestic Product (GDP) and matched with the topic of the research. As expected, the absolute majority of studies/trials are carried on by high-income countries, respectively 86% vs 14%; even if a slight prevalence of retrospective was recorded in both income groups, nonetheless the most part of prospective studies are carried out by high-GDP countries, 85% vs 15%. Finally the differences in the design of the study are understandable when considering the topic of the research.

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71 **Introduction and aims**

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73   We generally consider time as a quantity that in clinical studies/trials plays the role of

74   independent variable having, often, a real value on an axis of a graph; but time is just a way to

75   give order to changes and, in biology, time is essentially rhythm of changes, with short and long

76   cycles that are controlled by specific allocated resources that are the matter of chronobiology[1].

77   Usually clinical studies/trials are focused on diseases that are a common cause of

78   chronodisruption at multiple levels[2], meaning that circadian rhythms are severely altered among

79   the patients, depending on the severity of the disease; this disruption expands from the cellular

80   level, where the genes that regulate the biological clock are expressed, up to the subjective

81   perspective of the patient including pain. These studies are generally aimed at identifying causes

82   of disease and to set up/verify possible strategies to prevent or care them[3]. Usually the

83   observation of the variable(s) under study is fixed on singular time points or is followed

84   backward or forward in the so called, respectively, retrospective and prospective design of the

85   study. In such view the availability of comprehensive clinical databases, e.g. compiled during the

86   hospitalization, allows the clinical researcher to force easily backward the arrow of time in

87   search of possible causal links. This approach, that is undoubtedly cheaper, has often been

88   criticized[4] for the possible sources of errors due to bias and confounding, that are, indeed, more

89   common if compared with prospective studies[5].

90   In order to evaluate the tendency of researchers to use a retrospective design in

91   studies/trials by turning backward the "arrow of time", in this study we firstly searched

92   MEDLINE and obtained the number of retrospective and prospective matching studies, starting

93   from 1960 to 31 December 2017, an interval that was considered representative since, before

94   1960, very few studies are available. Secondly, in order to speculate on the reasons of this

95   choice, we randomly choose a sub-sample of studies, where the country of origin of the first

96   author was clearly stated, that was matched with the nominal Gross Domestic Product (GDP)

97   obtained from the World Economic Outlook (WEO) by the International Monetary Fund (IMF)[6].

98   Thirdly, to evaluate the prevalence of retrospective versus prospective studies in the different

99   thematic areas, the results have been grouped accordingly. Finally, in the discussion the

100 conclusions are matched with the opinions previously gathered through a random sample of

101 researchers, matching as authors of the papers retrieved, that were obtained by e-mailing, by

102 using a published survey questionnaire[7].

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108 **Methods**

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110   The MEDLINE database was queried through PubMed, the public access web portal of

111 the National Library of Medicine, National Institutes of Health-USA, in September 2017 by

112 using the keywords "retrospective study" and "prospective study"; these words were assumed as

113 reference to describe the two types of approach. For the purpose of this research, after

114 evaluating/comparing the possible strategies, including a comparison with other databases such

115 as EMBASE, (see also limitations of the study), in agreement with our reference librarian, we

116 relied on free text search by using the "best match", a function available on PubMed[8] that

117 includes MESH. The search string used was:

118   (retrospective study AND ("1960/01/01"[PDat] : "2017/12/31"[PDat]))
119   (prospective study AND ("1960/01/01"[PDat] : "2017/12/31"[PDat]))
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121 For the general statistics, even if few matching records were found starting from 1913, the

122 "publication date" of the search query was limited by starting from 1960, where at least 10

123 matching documents for both category were found. For the assessment of the country of origin

124 and topic, we randomly sampled a minimum of 5 studies per decade where the country of origin

125 of the first author was clearly stated and the topic was assessable by the availability of a full text.

126   Since in most cases it was not possible to find all the information needed, this sample was built

127   starting from 2004 and placed in a comprehensive database including the over-mentioned

128   variables.

129   Finally, we created two GDP-based macro-categories that permitted to distinguish high-

130   income countries of origin of the research from low ones; the cut-off for incomes was > 467,775

131   millions of US $; this arbitrary value, corresponding to 75% over the mean, allowed to include a

132   larger number of countries into the high-GDP with respect to other criteria such as the G-7. Thus

133   the two GDP categories were matched with the topic of the studies.

134   MMC and PV defined the search strategy, in agreement with our reference librarian (see

135   acknowledgments section), PV performed the search strategy. All the disagreements were solved

136   by carefully checking the search strategy previously.

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139   **Results**

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141   The results support that, since the sixties, there are significant numerical differences with a

142   majority of retrospective studies. Out of a 1,438,872 matching records, 787,938 (55%) were

143   retrospective whereas 650,934 (45%) prospective. By examining the decades, this trend began in

144   1960 and, except for the decade 1980-1990, is maintained and widen considerably in the last

145   years. Indeed, in the last 5 years 278,354 (58.6%) retrospective vs 196,679 (41.4%) prospective

146   studies were found, corresponding to a difference of +81,675 retrospective studies (Figure 1).

147   Furthermore, as stated in the methods section, even if the search was limited to the interval 1960-

148   2017, a difference is appreciable since the starting coverage of the database; the keywords

149   "retrospective study" appears for the first time in 1913 while "prospective study" in 1923, with

150   only one matching document for each type of study. This difference is also reproduced in the

151   sub-sample (years 2004-2015) made of 1576 matching records, of which 903 (57%) were

152   retrospective whereas 673 (43%) prospective. The general prevalence of studies attributable to

153   the high-GDP countries was very high accounting for 86% of the total vs 14%; this data support

154   that conception, realization of a clinical study/trial and access to publication is related to the

155   GDP (**Figure 2**). Furthermore the 85% of prospective studies are ascribable to the high-GDP

156   group while only a 15% to the low-GDP, and this even if a prevalence of retrospective studies

157 was recorded in the high-GDP. Finally these differences are understandable when considering
158 the topic of the research that requires a specific design (**Figure 3**).

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160 **Discussion**

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162   Time is the most intriguing variable in the universe and, on earth, it affects irreversibly
163 biological life since every form of life has a non-zero probability of dying that increases with the
164 flow of time in a general process known as biological aging. Since it is impossible to reverse the
165 course of events, living organisms must adapt reproduction, development and evolution to cope
166 time and its rhythms by committing specific biological resources that are the matter of
167 chronobiology, making time a measure of the cyclical and stochastic changes in biology rather
168 than an absolute physical quantity. Biological life with aging is invariably associated with the
169 experience of disease, whose incidence seems to be ruled by chance[9] but when clinical
170 researchers study diseases, generally, to preserve human life and avoid unnecessary suffering,
171 what they actually do of the time variable, namely, how the variables are followed, or sampled,
172 in time, backward or forward? Indeed any study on diseases might takes into account the "point
173 of view" which might suggest misleading cause-effect relationship[10]. Even if the our objective
174 was not so ambitious to dismantle the mechanism of time in diseases, in the present study, based
175 on a MEDLINE search strategy starting from 1960, we highlighted that, when studying disease,
176 the preferred choice of the study design is the retrospective one and this is nontrivial as it allows
177 us to make some considerations. We can assume that the retrospective study design is prevalent
178 in the scientific literature possibly since it represent: 1) a cheaper approach to make forecasting
179 on disease development, 2) an easy choice because of the availability of clinical records or,
180 simply, 3) a wrong choice due to lack of statistical knowledge. These assumption are
181 corroborated by the opinions of a random sample of researchers, matching as authors of the
182 papers retrieved, that were obtained by e-mailing, previously, by using a published survey
183 questionnaire[7]. In particular, in choosing the retrospective design, the involved researchers feel
184 that they have been limited by the availability of funds and instead favored by the easy access to
185 a clinical database. Furthermore, the surveyed researchers believe that the prospective design is
186 more expensive, statistically appropriate and clinical predictable. At this regard, it should be said
187 that there is no direct evidence of the inferiority of retrospective studies if well conducted[11];

188 however, retrospective studies are limited by the level of knowledge and availability of data at
189 the time of collection, on the contrary, prospective studies may, theoretically, incorporate any
190 possible newer variable. These opinions are supported by our results since the absolute majority
191 of studies/trials are almost always conducted by high-GDP countries and the 85% of prospective
192 studies are ascribable to the high-GDP group while only a 15% to the low-GDP. A further key
193 can be found in the topic of the studies/trials where most of prospective are associated with
194 "cardiovascular", a topic known to catalyze great investments from the pharmaceutical
195 companies, and "surgery", which benefits from a short-term prospective outcome.

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198 **Conclusions**

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200   In Clinical studies/trial the time variable is fundamental in the design the study; by
201 analyzing MEDLINE database 1960-2017: 1- most of clinical studies/trial use a retrospective
202 design of the study even if there is no direct evidence of its superiority if compared to the
203 prospective one, on the other hand, there are no evidence of an intrinsic inferiority of the
204 retrospective design in statistical precision and in clinical predictability[11]; 2- most of prospective
205 studies were conducted by high-GDP countries supporting that the cost is, as expected, one of
206 the main constraints and this possibly concerns the cost of research, as also highlighted by other
207 studies, of some years ago, on imbalance in health research resources[12] and on the consequences
208 of globalization of clinical research[13]; 3- some research topics are more frequently associated
209 with the perspective design and this may be linked, possibly, to the availability of funds and to
210 the need of a specific short-term design of the study.

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212 **Limitations**

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214   This study has several limitations that should be acknowledged, Firstly, the key words
215 *retrospective* and *prospective* are assumed as reference to describe two approaches in setting up a
216 clinical study/research and this may results in some imprecisions due to a broad use of these
217 terms; at this regard the long lasting use of this terminology confirms their established semantic
218 use. Secondly, bibliometric methods examine a body of work at a macro level and our results

219 must be interpreted in light of this. Using a simple search has the benefits of being readily
220 understood and easily replicated but inevitably produces some imprecision or noise. In our study
221 93% of prospective studies and 95% of retrospective studies were indexed as human, some were
222 index as animal studies, some were indexed as both human and animal studies, and some were
223 indexed as neither. In any case, these studies have been classified this way according to MESH
224 and, therefore, included in the results of the research which was conducted with a correct
225 syntax.As well, about 8% of prospective studies were also retrieved by the search for
226 retrospective studies and are included in both analyses; thirdly, MEDLINE is constantly
227 expanding thus our study represents a partial view over a rather long time interval. Finally, by
228 focusing on the first author, we emphasized the authorship by losing the opportunity to highlight
229 international collaborations.

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235 Milan, Italy.

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289 **Figure Legends**

290 **Figure 1.**

291 *Panel A: area graph showing the number of matching documents retrieved from MedLine years*

292 *1960-2017 by using the keywords indicated in the method section. On the x axis are reported the*

293 *decades starting from 1960, on the y axis, the absolute number of published papers. Panel B: pie*

294 *chart reporting the percentage of retrospective and prospective studies.*

295

296 **Figure 2.**

297 *Pie Chart showing the prevalence of Retrospective (left) vs Prospective Studies (right) in high*

298 *and low-GDP countries as retrieved from MedLine.*

299

300 **Figure 3.**

301 *Bar chart showing the prevalence of the topic in the Retrospective (panel A) and Prospective*

302 *Studies (panel B) as retrieved from MedLine.*

Figure 1

Number of matching documents retrieved from MedLine years 1960-2017 by using the keywords indicated in the method section.

A: area graph showing the number of matching documents retrieved from MedLine years 1960-2017 by using the keywords indicated in the method section. On the x axis are reported the decades starting from 1960, on the y axis, the absolute number of published papers. B: pie chart reporting the percentage of retrospective and prospective studies.
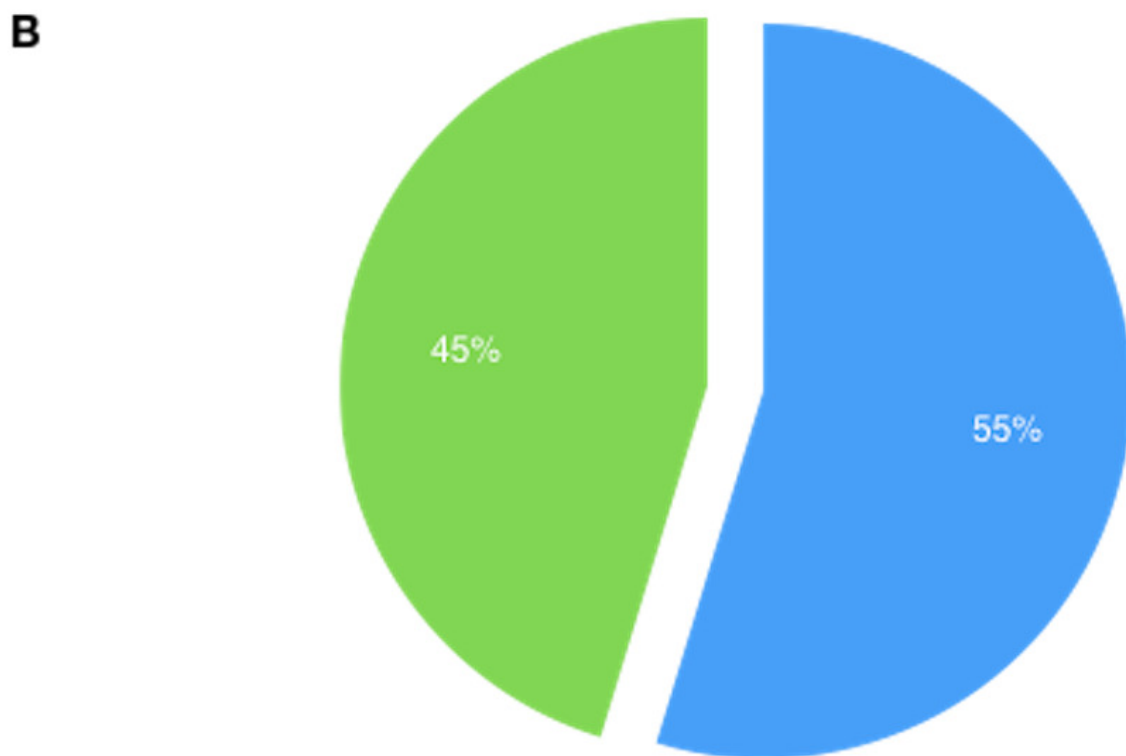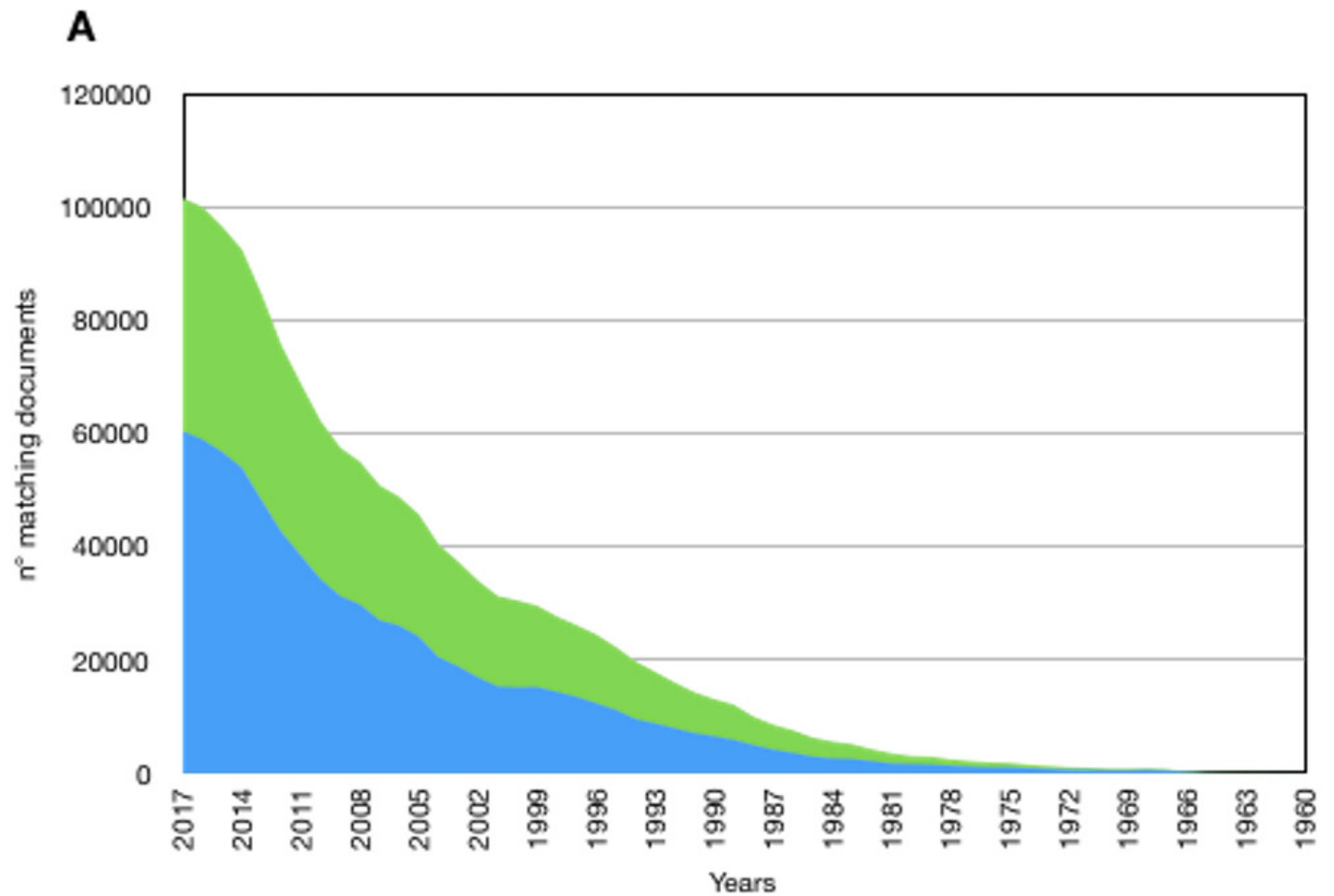
Figure 2

Pie chart showing the prevalence of Retrospective vs Prospective studies.

Pie chart showing the prevalence of Retrospective (A) vs Prospective studies (B) in high and low-GDP countries as retrieved from MEDLINE.
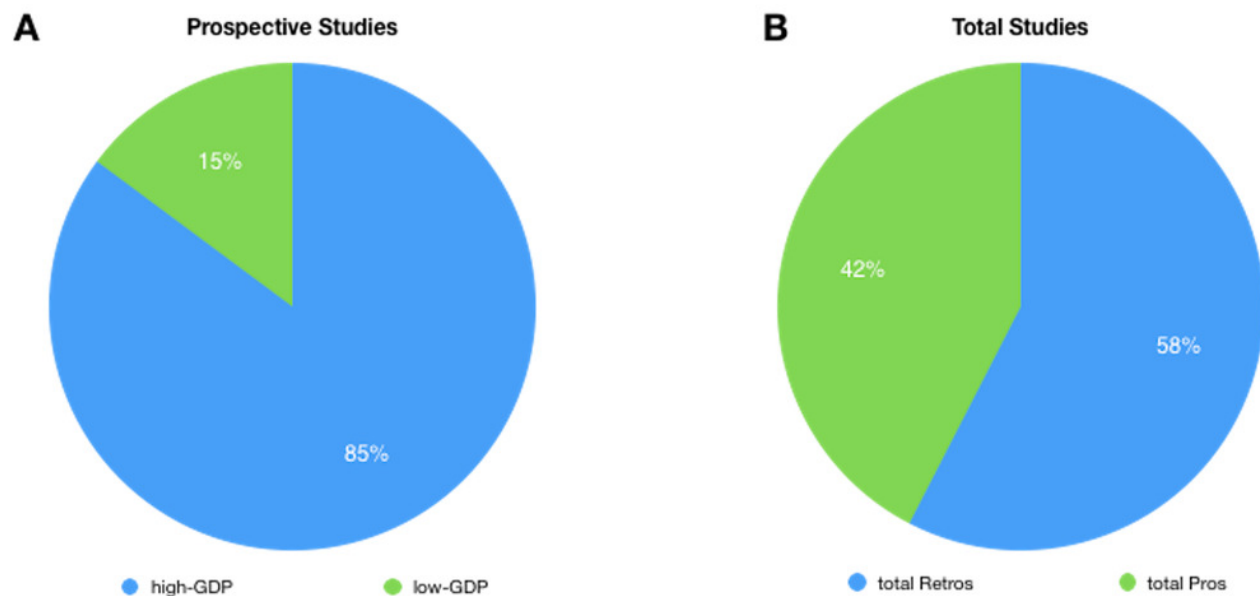
Figure 3

Prevalence of the topic in the Retrospective and Prospective Studies retrieved from MedLine.

Bar chart showing the prevalence of the topic in the Retrospective (A)and Prospective Studies (B) as retrieved from MedLine.