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SYSTEMATIC REVIEW AND META-ANALYSIS

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Impact of Modifiable Cardiovascular Risk Factors on Mortality After Percutaneous Coronary Intervention

A Systematic Review and Meta-Analysis of 100 Studies

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Abstract: Modifiable cardiovascular risk factors such as obesity, hypertension, dyslipidemia, smoking, diabetes mellitus, and metabolic syndrome can easily give rise to coronary heart disease (CHD). However, due to the existence of the so-called "obesity paradox" and "smoking paradox," the impact of these modifiable cardiovascular risk factors on mortality after percutaneous coronary intervention (PCI) is still not clear.

Therefore, in order to solve this issue, we aim to compare mortality between patients with low and high modifiable cardiovascular risk factors after PCI.

Medline and EMBASE were searched for studies related to these modifiable cardiovascular risk factors. Reported outcome was all-cause mortality after PCI. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated, and the pooled analyses were performed with RevMan 5.3 software.

A total of 100 studies consisting of 884,190 patients (330,068 and 514,122 with high and low cardiovascular risk factors respectively) have been included in this meta-analysis. Diabetes mellitus was associated with a significantly higher short and long-term mortality with RR 2.11; 95% CI: (1.91–2.33) and 1.85; 95% CI: (1.66–2.06), respectively, after PCI. A significantly higher long-term mortality in the hypertensive and metabolic syndrome patients with RR 1.45; 95% CI: (1.24–1.69) and RR 1.29; 95% CI: (1.11–1.51), respectively, has also been observed. However, an unexpectedly, significantly lower mortality risk was observed among the smokers and obese patients.

Certain modifiable cardiovascular risk subgroups had a significantly higher impact on mortality after PCI. However, mortality among the obese patients and the smokers showed an unexpected paradox after coronary intervention.

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Abbreviations: BMI = body mass index, CAD = coronary artery disease, DM = diabetes mellitus, LDL = low-density lipoprotein, MS = metabolic syndrome, PCI = percutaneous coronary intervention.

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INTRODUCTION

Coronary heart disease, also known as coronary artery disease (CAD), is the most common type of heart disease in the elderly. Almost all over the world, it is the number 1 cause of death in both men and women. From the year 1990 to 2013, there has been a rise from 5.74 to 8.14 million deaths from CAD globally.[1] There are many risk factors associated with CAD. These risk factors include hypertension, dyslipidemia, smoking, obesity, old age, family history, diabetes mellitus (DM), and metabolic syndrome (MS).[2] These risk factors can still be subdivided into modifiable and nonmodifiable risk factors. Modifiable risk factors are those that can be changed; or simply, if careful precautions are taken, the risk for developing CAD will be lower in the susceptible population. For example, eating a healthy diet, doing regular exercises, avoiding smoking, and maintaining a healthy weight are all safety measures which can help to prevent CAD.[3,4] Except old age and a family history with cardiovascular disorders, factors such as a high body mass index (BMI), hypertension, dyslipidemia, smoking, DM, and MS are all considered as modifiable cardiovascular risk factors.

Unfortunately, because of the unhealthy lifestyle adopted by people nowadays, they finally end up with conditions which expose them to a high risk for CAD. When symptoms become more severe, or intolerable, and when medications become ineffective, percutaneous coronary intervention (PCI) proves to be the most common invasive treatment in these patients.[5] However, due to the presence of the so-called phenomenon "obesity paradox" and "smoking paradox" whereby the mortality rate in the obese patients and smokers is unexpectedly lower compared to the normal weight patients and nonsmokers, respectively, the impact of these modifiable cardiovascular risk factors on mortality after PCI is still not clear. Therefore, in order to solve this issue, we aim to compare the short- and long-term mortality in patients with low and high modifiable cardiovascular risk factors after PCI.

METHODS

Data Sources and Search Strategy

Medline and EMBASE were searched for randomized controlled trials (RCTs) and observational studies by typing the words or phrases "X and percutaneous coronary intervention/PCI" whereby X was interchangeable with these modifiable cardiovascular risk factors such as smoking, overweight/obesity/high BMI, hypertension, hyperlipidemia/hypercholesterolemia/high-density lipoprotein (HDL)/low-density lipoprotein (LDL), DM, and MS. To further enhance this search, the term "angioplasty" has also been used to replace PCI and the words "smoking paradox" and "obesity paradox" have been used to replace smoking and obesity, respectively. No language restriction was applied.

Inclusion and Exclusion Criteria

Studies were included if:

(1) They were RCTs or observational studies relating these modifiable cardiovascular risk factors with PCI.
(2) They reported mortality among their clinical endpoints.
(3) They included data for both the experimental and the control groups. For example, DM and non-DM, smokers and nonsmokers, overweight/obese and nonobese/normal weight, MS and non-MS, hypertensive and normotensive patients, increased LDL and normal/low LDL, or decreased high density lipoprotein (HDL) and increased HDL.

Studies were excluded if:

(1) They did not include these modifiable cardiovascular risk factors.
(2) They were meta-analyses, case studies, or letter to editors.
(3) No control group was present.
(4) Mortality was not among the reported endpoints.
(5) Duplicates.

Types of Participants

All the patients were >18 years old and suffered from CAD. Enrolled patients in the experimental group had at least 1 modifiable cardiovascular risk factor (diabetes, MS, high BMI, dyslipidemia, cigarette smoking, or hypertension) whereas those patients in the control group did not suffer from the risk factor being analyzed in the corresponding subgroups. All patients underwent PCI.

Definitions, Outcomes, and Follow-Up Periods

Modifiable Cardiovascular Risk Factors: defined as cardiovascular risk factors that can be controlled or if prevented, can result in a lower risk of suffering from CAD. In our studies, these patients were considered as high risk patients. Low risk patients, who acted as controls for this meta-analysis, were those without these modifiable cardiovascular risk factors.

DM: defined as a fasting blood glucose (FBG) level of >7.0 mmol/L or an oral glucose tolerance test (OGTT) >11.1 mmol/L observed at least on 2 different occasions.

Overweight and obese: BMI of >25 and >30 kg/m^2, respectively.

Hypertension: a blood pressure of >130/80 mmHg on at least 2 separate occasions.

Dyslipidemia: defined as an LDL level of (>130 mg/dL) or an HDL level of (<40 mg/dL). A borderline value was already considered as dyslipidemia in this study.

MS: a condition diagnosed if at least 3 of the followings were present: central obesity, high blood pressure, high fasting plasma glucose, high serum triglyceride, and low-high-density lipoproteins.

Smoking: included current smokers and late nonsmokers. Quitters, former smokers, pre- and post-PCI smoking quitters have not been included in the study.

In-hospital mortality: included all-cause deaths during the hospital stay (≤30 days).

Short-term mortality: included all-cause deaths during a follow-up period from 30 days to 1 year after PCI.

Long-term mortality: included all-cause deaths during a follow-up period at 1 year or more than 1 year after PCI.

Data Extraction and Quality Assessment

Two authors (PKB and ZW) independently reviewed the data and assessed the eligibility and methodological quality of each eligible study. Information and data regarding the number of patients and patient characteristics, associated risk factors, intervention strategies, and the clinical outcomes, and respective follow-up periods (in-hospital, short-term, and long-term) were systematically extracted. If any of the 2 authors disagreed about the information or data extracted, disagreements were discussed between the authors, and if the authors could not reach a final decision, disagreements were resolved by the 3rd author (MHC). The bias risk of trials was assessed with the components recommended by the Cochrane Collaboration.[6]

Methodological Quality and Statistical Analysis

Study selection, data collection, analysis, and reporting of the results were performed using the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Heterogeneity across trials was assessed using the Cochrane Q-statistic ($P \leq 0.05$ was considered significant) and I^2-statistic. I^2 described the percentage of total variation across studies, that is, due to heterogeneity rather than chance. A value of 0% indicated no heterogeneity, and larger values indicated increased heterogeneity. If I^2 was <50%, fixed effect model was used. However, if I^2 was >50%, a random effect model was used. Publication bias was visually estimated by assessing funnel plots. We calculated risk ratios (RRs) and 95% confidence intervals (CIs) for categorical variables. The pooled analyses were performed with RevMan 5·3 software. Since this is a systematic review and meta-analysis, ethical approval was not required.

RESULTS

Selection of Studies for This Meta-Analysis

A total of 7456 articles were identified from search databases, and 32 articles were identified from references. After excluding the 1120 duplicates, 6030 articles were excluded by title and abstract since they were not related to our topic. Among the remaining articles, 79 were related to obesity, 142 to diabetes, 25 to MS, 36 to dyslipidemia, 29 to smoking, and 27 were related to hypertension. A total of 338 full text articles were assessed for eligibility. More articles were excluded since they were meta-analyses, case studies, data for the control group were not available, outcomes of interest were not reported and also dichotomous data which were very important for our statistical analysis were not provided. The flow diagram for the selection of studies has been represented in Figure 1.

A total number of 100 articles from randomized controlled trials and observational studies have been included in this meta-analysis with a total number of 844,190 patients to be analyzed; among which, 330,068 patients were in the experimental group while 514,122 were in the control group. The total number of patients associated with the corresponding risk factors from this whole study have been given in Tables 1 and 2 shows the total number of patients in all the different subgroups (for both the experimental and control groups) as well as their follow-up periods.

Among these 330,068 patients analyzed in the experimental group, 76.2% had hypertension, 24% were smokers, 50.3% had dyslipidemia, 65.5% were overweight or obese, 1.5% had MS, and 47.6% had DM.

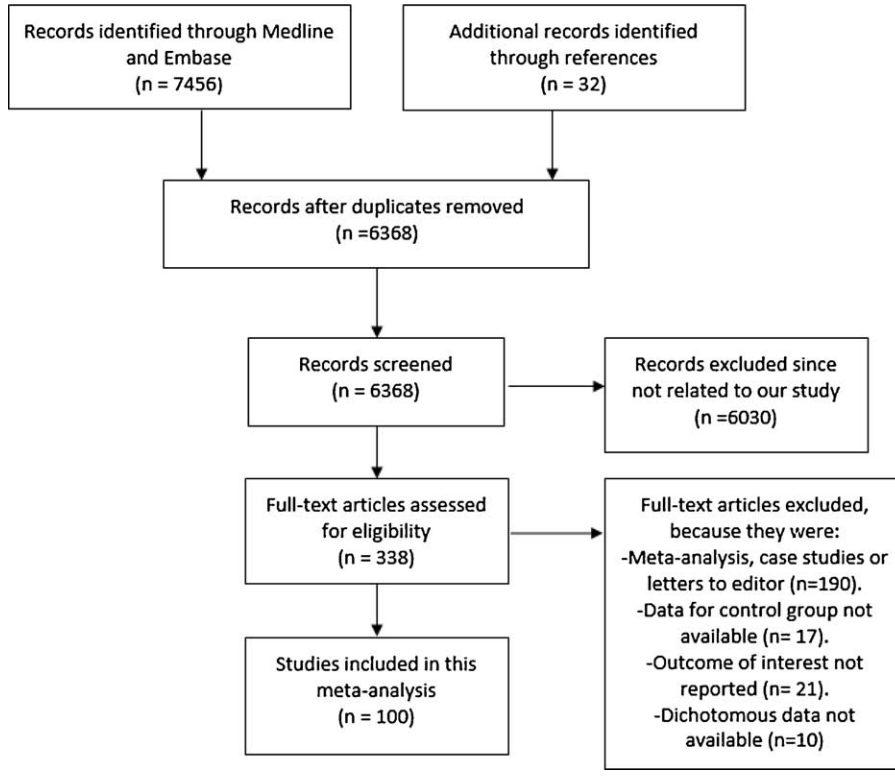


FIGURE 1. Shows the flow diagram for the study selection.

Considering this whole study, pure data for only 27,415 (10.9%) hypertensive patients, 14,507 (18.3%) smokers, 15,008 (9.03%) patients with dyslipidemia, 215,834 (99.9%) patients with high BMI, 4741 (94.8%) patients with MS, and 52,563 (33.4%) patients with DM were available for subgroup analysis. Note that data which were not available in the original articles have been omitted.

Table 2 has been divided into different subgroups of modifiable cardiovascular risk factors. Total number of patients in the experimental group, control group as well as the total number of patients in each study with their follow-up periods have been given in Table 2. Five studies dealt with hypertension, 8 studies dealt with smoking, 6 studies dealt with dyslipidemia, 9 studies dealt with MS, 23 studies dealt with high

TABLE 1. An Approximation* of the number of patients corresponding to these modifiable risk factors throughout this whole meta-analysis

Features	Number of Patients (n)	(%)
Patients in this study	844,190	
Patients in the experimental group	330,068	39.1%
Patients in the control group	514,122	60.9%
Modifiable cardiovascular risk factors in the experiment group	Number of patients analyzed/number of patients with corresponding risk factor in whole study	
Hypertension	27,415/251,567	10.9%
Smoking	14,507/79,205	18.3%
Dyslipidemia	15,008/166,173	9.03%
Overweight and obesity	215,834/216,041	99.9%
Metabolic syndrome	4741/4999	94.8%
Diabetes	52,563/157,160	33.4%

* These data were calculated according to data provided in these 100 studies. The data concerning the number of patients with their corresponding risk factor in the whole study were also obtained from the baseline features of each study. However, studies without dichotomous data at baseline, or if corresponding data were not available, have been omitted from this count. Therefore, except the data analyzed, the count for ''modifiable cardiovascular risk factors for the whole study'' is just an approximation for this study.

TABLE 2. The Number of Patients in These Different Subgroups and the Corresponding Follow-Up Periods

Study	Hypertensive Patients (n)	Normotensive Patients (n)	Total No of Patients (n)	Follow-Up Period
Lee 2012[7]	1218	1220	2438	In hospital, short and Long-term
Lingman 2011[8]	22,499	20,673	43,172	Short-term
Luca 2013[9]	700	962	1662	Short-term
Luca 2014[10]	2764	3522	6286	Long-term
Rembek 2010[11]	234	132	366	In hospital
Study	Smoker (n)	Nonsmoker (n)	Total no of patients (n)	Follow-up period
Arbel 2014[12]	3201	1363	4564	Short and long-term
Chen 2012[13]	4049	7611	11,660	Long-term
Goto 2011[14]	1563	1765	3328	Short and long-term
Liu 2013[15]	147	226	373	Long-term
Mohamedali 2013[16]	258	501	759	Short-term
Robertson 2014[17]	3943	9614	13,557	Short and long-term
Tan 2014[18]	448	603	1051	Short and long-term
Weisz 2015[19]	898	638	1536	Short and long-term
Study	Dyslipidemia (n)	Normal lipids (n)	Total no of patients (n)	Follow-up period
Cho 2010[20]	3284	6287	9571	In hospital, short and Long-term
Ghazzal 2009[21]	2113	1975	4088	Long-term
Izuhara 2015[22]	3838	6553	10,391	Long-term
Ji 2015[23]	4030	5026	9056	In hospital, short-term
Kini 2009[24]	1521	2095	3616	Long-term
Seo 2011[25]	1585	1108	2693	Long-term
Study	Metabolic syndrome (n)	Nonmetabolic syndrome (n)	Total no of patients (n)	Follow-up period
Butler 2006[26]	1169	1866	3035	Short-term
Kasai 2006[27]	318	430	748	Long-term
Kasai 2008[28]	318	430	748	Long-term
Kim 2010[29]	170	168	338	Short and long-term
Lee 2015[30]	570	333	903	Long-term
Maron 2011[31]	1362	886	2248	Long-term
Marso 2012[32]	239	434	673	Long-term
Patsa 2013[33]	147	364	511	Long-term
Rana 2005[34]	448	453	901	Short-term
Study	Overweight and obese (n)	Normal and underweight (n)	Total no of patients (n)	Follow-up period
Akin 2012[35]	4370	1436	5806	In hospital, short-term
Ellis 1996[36]	2841	614	3455	In hospital
Gruberg 2002[37]	7710	1923	9633	In hospital and long-term
Gruberg 2005[38]	431	168	599	Long-term
Gurm 2002[39]	1553	537	2090	Long-term
He 2015[40]	528	549	1077	In hospital and long-term
Kaneko 2013[41]	473	732	1205	Long-term
Kang 2009[42]	2442	1382	3824	In hospital, short and Long-term
Kosuge 2008[43]	980	2096	3076	In hospital
Lancefield 2010[44]	3442	1320	4762	In hospital, short and long-term
Mehta 2007[45]	1622	703	2325	In hospital and long-term
Minutello 2004[46]	69,501	25,934	95,435	In hospital
Nikolsky 2005[47]	1074	233	1307	Long-term
Numasawa 2015[48]	3735	6407	10,142	In hospital
Park 2013[49]	10,749	12,432	23,181	Long-term
Payvar 2013[50]	83,861	217,616	301,477	In hospital
Poludasu 2008[51]	631	146	777	In hospital
Poston 2004[52]	1211	391	1602	Long-term
Powell 2003[53]	4763	1269	6032	In hospital
Sarno 2010[54]	1204	497	1701	Long-term
Shubair 2006[55]	3645	986	4631	In hospital
Wang 2012[56]	4491	1592	6083	Long-term
Witassek 2014[57]	4577	2361	6938	In hospital
Study	Diabetics (n)	Non-diabetics (n)	Total no of patients (n)	Follow-up period
Abizaid 1998[58]	248	706	954	In hospital and short-term
Akin 2010[59]	1659	3559	5218	In hospital and long-term
Antoniucci 2004[60]	166	895	1061	Short-term
Banning 2010[61]	225	662	887	Long-term
Billinger 2008[62]	201	811	1012	Long-term
Blondal 2012[63]	297	1355	1652	In hospital and long-term
Claessen 2011[64]	265	860	1125	Long-term
Daemen 2008[65]	159	448	607	Long-term
Elezi 1998[66]	715	2839	3554	In-hospital

Study	Hypertensive Patients (n)	Normotensive Patients (n)	Total No of Patients (n)	Follow-Up Period
Fernandez 2011[67]	141	193	334	Long-term
Garg 2008[68]	5051	12,742	17,793	Long-term
El Ghannudi 2011[69]	163	273	436	Short-term
Harjai 2003[70]	626	3116	3742	In hospital and short-term
Hasdai 2000[71]	99	466	565	In hospital and short-term
Hermillier 2005[72]	318	996	1314	Short-term
Jain 2015[73]	2563	5269	7832	Short-term
Jensen 2010[74]	1575	10,772	12,347	Short and long-term
Jensen 2012[75]	390	2384	2774	Long-term
Kassaian 2012[76]	703	2181	2884	Short-term
Kedhi 2014[77]	3167	3167	6334	Short and long-term
Kereiakes 2010[78]	1185	2498	3683	Long-term
Kip 1996[79]	281	1833	2114	In hospital and long-term
Kirtane 2008[80]	827	2686	3513	Long-term
Kirtane 2009[81]	477	1071	1548	Long-term
Kufner 2014[82]	162	288	450	Long-term
Kumar 2007[83]	297	541	838	Short-term
Kuramitsu 2013[84]	452	140	592	Long-term
Lee 2006[85]	263	965	1228	Long-term
Lee 2012[7]	921	1517	2438	In hospital, short and long-term
Lenzen 2006[86]	1877	947	2824	Short-term
Lima 2013[87]	64	141	205	Long-term
Lingman 2011[8]	9415	34,278	43,693	In-hospital
Maeng 2011[88]	337	1995	2332	Long-term
Marui 2015[89]	1065	1123	2188	Long-term
Mathew 2004[90]	2684	8798	11,482	Short-term
Mehran 2004[91]	195	560	755	In hospital
Muhlestein 2003[92]	394	630	1024	Long-term
Muramatsu 2014[93]	136	415	551	Long-term
Norhammar 2004[94]	299	2158	2457	Long-term
Onuma 2011[95]	271	957	1228	Long-term
Overgaard 2013[96]	203	898	1101	Long-term
Park 2009[97]	865	2295	3160	Long-term
Silber 2013[98]	878	1903	2781	Long-term
Sohrabi 2011[99]	34	129	163	In hospital and short-term
Stein 1995[100]	1133	9300	10,433	In hospital
Stone 2011[101]	1869	4911	6740	Long-term
Syed 2010[102]	161	395	556	Long-term
Tada 2011[103]	3404	6378	9782	Long-term
Weber 2008[104]	1948	4707	6655	In hospital and short-term
Wilson 2004[105]	1142	3142	4284	In hospital
Witzenbichler 2011[106]	593	3006	3599	Short-term

BMI, and 51 studies dealt with DM. Two studies were common in both the hypertension and the diabetic groups since they analyzed both diabetic and hypertensive patients together. Follow-up periods were classified as in-hospital, short-term, and long-term follow-ups as mentioned in the "definition" section.

The baseline characteristics of all the included studies have been represented in Table 3.

Patients in the hypertensive group were older than the normotensive patients. There were more male patients in the control group compared to the experimental group. DM and dyslipidemia were more prominent among the hypertensive patients whereas cigarette smoking was more common in the control group.

Majority of the smokers were males and they were younger than the nonsmokers. Apart from 1 study, hypertension was more prominent among the nonsmokers. Most of the nonsmokers suffered from DM too.

Patients from both the experimental and the control groups were almost similar in age. If analyzed as a whole, there was no significant differences between genders, hypertension, and smoking between these 2 groups. However, except from 1 study, DM was more prominent among those with dyslipidemia.

There was no significant difference in age between these 2 groups. Majority of those patients in the control group were males. Hypertension was more prominent in the experimental group. Smoking was almost similar in both groups. Except from 1 study which had no diabetic patients and 1 which had less patients with DM, DM was more common in the MS group.

The overweight and obese patients were younger than the normal weight and underweight patients. There were more males than females in the experimental group. Hypertension, dyslipidemia, and DM were more prominent in the experimental group. Most of the patients in the high BMI category were nonsmokers.

There was no significant difference in age between the diabetic and nondiabetic patients. Most of the patients in the control group were males. Hypertension and dyslipidemia were more prominent in the DM group. Most of the patients in the experimental group were nonsmokers.

TABLE 3. Shows the Baseline Features of Each of the Included Studies

Studies	Age	Men	HT	Ds	Cs	DM
Hypertension group	E/C	E/C	E/C	E/C	E/C	E/C
Lee 2012[7]	67.8/61.6	59.7/78.7	100.0/0.0	5.9/4.0	46.1/68.5	–
Lingman 2011[8]	68.0/65.5	68.5/74.5	100.0/0.0	–	15.0/24.0	29.4/13.1
Luca 2013[9]	63.0/59.5	71.6/81.3	100.0/0.0	45.6/30.0	43.0/58.1	23.6/12.1
Luca 2014[10]	62.9/59.0	72.4/80.3	100.0/0.0	50.0/27.4	41.0/53.9	21.7/10.6
Rembek 2010[11]	–	–	100.0/0.0	56.4/43.2	57.3/72.2	26.5/13.6
Smoking group	E/C	E/C	E/C	E/C	E/C*	E/C
Arbel 2014[12]	59.7/68.0	79.0/37.0	43.7/55.0	56.3/44.0	100.0/0.0	26.3/35.0
Chen 2012[13]	53.1/60.9	96.0/55.6	44.7/54.3	32.0/31.7	100.0/0.0	17.2/20.6
Goto 2011[14]	55.0/66.0	79.7/75.1	44.5/60.1	39.0/46.5	100.0/0.0	12.5/19.7
Liu 2013[15]	53.8/61.0	–	61.2/58.2	60.5/48.8	100.0/0.0	25.9/29.1
Mohamedali 2013[16]	61.0/68.0	99.2/98.4	–	50.0/41.0	100.0/0.0	30.0/44.0
Robertson 2014[17]	55.7/65.3	74.8/68.1	55.7/71.4	48.1/60.8	100.0/0.0	20.6/31.0
Tan 2014[18]	54.0/60.0	82.4/77.4	25.2/38.8	26.1/29.0	100.0/0.0	10.0/18.2
Weisz 2015[19]	53.0/65.0	76.6/61.9	41.0/51.7	35.2/40.9	100.0/0.0	13.4/18.8
Dyslipidemia group	E/C	E/C	E/C	E/C	E/C*	E/C
Cho 2010[20]	60.5/64.0	67.5/75.0	45.0/50.3	100.0/0.0	58.0/60.0	23.5/30.0
Ghazzal 2009[21]	63.4/66.2	82.9/58.4	77.8/79.7	100.0/0.0	20.7/14.9	33.7/25.6
Izuhara 2015[22]	68.4/67.6	63.0/77.0	83.0/82.0	100.0/0.0	34.0/31.0	41.0/35.0
Ji 2015[23]	65.4/62.1	61.3/81.5	53.3/45.8	100.0/0.0	53.5/65.2	33.3/23.6
Kini 2009[24]	66.1/69.5	79.2/57.3	89.7/88.7	100.0/0.0	18.1/14.2	44.6/41.4
Seo 2011[25]	62.7/62.2	59.7/75.2	62.6/56.8	100.0/0.0	23.6/26.2	41.0/30.7
Metabolic syndrome group	E/C	E/C	E/C	E/C	E/C	E/C
Butler 2006[26]	73.5/73.7	48.5/43.0	51.4/64.7	29.5/62.2	10.3/7.8	15.3/30.7
Kasai 2006[27]	59.0/59.0	85.2/88.4	78.3/54.9	–	78.3/76.7	59.4/25.3
Kasai 2008[28]	59.1/60.3	85.1/87.4	78.2/52.8	–	78.2/76.3	59.4/25.3
Kim 2010[29]	63.5/62.3	60.0/71.4	80.0/31.0	–	43.5/52.4	47.1/18.5
Lee 2015[30]	64.8/64.8	61.6/76.9	69.1/46.8	–	21.6/25.8	47.4/14.4
Maron 2011[31]	61.2/63.7	85.1/88.7	79.6/50.5	–	28.2/25.9	47.4/13.7
Marso 2012[32]	56.6/59.9	71.1/76.2	60.9/47.7	46.3/49.0	46.8/44.8	0.0/27.4
Patsa 2013[33]	59.8/61.8	78.2/84.6	65.3/59.1	76.2/66.5	74.8/72.5	40.8/26.9
Rana 2005[34]	61.0/63.0	71.0/72.0	–	–	21.0/18.0	24.0/7.0
High BMI group	E/C	E/C	E/C	E/C	E/C	E/C
Akin 2012[35]	64.6/66.1	75.3/69.8	87.7/75.4	82.3/75.9	20.9/26.3	38.1/21.5
Ellis 1996[36]	60.5/65.0	65.4/65.0	55.4/45.3	21.0/14.5	20.3/20.8	16.4/10.1
Gruberg 2002[37]	62.5/68.0	69.8/59.7	67.7/55.6	72.5/63.1	58.2/54.3	31.8/17.4
Gruberg 2005[38]	60.5/61.0	76.5/70.8	49.1/37.5	60.8/51.8	24.3/37.0	24.8/8.90
Gurm 2002[39]	–	69.3/61.0	56.7/43.0	–	20.7/37.0	26.3/11.0
He 2015[40]	–	63.0/64.7	74.6/53.1	50.8/46.9	14.2/19.1	25.6/22.9
Kaneko 2013[41]	59.2/68.7	90.4/71.2	70.7/55.1	69.1/47.9	52.1/29.2	42.0/27.1
Kang 2009[42]	58.0/67.2	78.0/66.9	50.7/36.6	11.6/8.40	65.2/59.6	26.1/19.9
Kosuge 2008[43]	60.0/70.0	74.5/67.0	64.0/53.5	47.0/26.5	51.5/43.0	37.5/26.0
Lancefield 2010[44]	62.5/68.1	72.2/66.8	70.0/58.3	74.3/63.7	22.1/25.2	29.8/14.8
Mehta 2007[45]	58.5/63.0	76.0/67.0	51.0/39.0	40.5/33.0	42.0/47.0	19.0/11.0
Minutello 2004[46]	59.4/66.1	62.8/55.4	68.0/57.6	–	26.2/25.9	29.2/14.3
Nikolsky 2005[47]	61.7/65.8	73.5/65.2	72.1/68.3	67.5/60.7	22.4/22.7	26.9/10.3
Numasawa 2015[48]	62.3/72.1	81.1/68.0	82.5/69.8	75.7/55.7	41.7/29.8	52.5/36.9
Park 2013[49]	60.0/65.0	65.7/67.0	64.3/47.3	46.7/34.3	29.3/32.5	33.0/25.5
Payvar 2013[50]	60.0/69.0	53.0/63.0	90.0/76.0	83.0/75.0	–	61.0/33.0
Poludasu 2008[51]	61.8/66.0	53.1/56.8	88.8/89.7	–	23.3/33.5	51.5/45.9
Poston 2004[52]	63.0/69.0	72.2/44.2	69.7/65.9	–	23.3/33.5	29.8/17.8
Powell 2003[53]	64.7/70.5	69.3/54.0	65.3/55.5	67.7/49.5	19.3/28.5	28.0/15.0
Sarno 2010[54]	63.9/65.9	75.5/71.0	77.5/65.0	70.5/60.0	24.5/27.0	30.0/15.0
Shubair 2006[55]	58.9/65.2	65.9/64.5	65.8/54.5	84.1/77.6	23.7/20.6	29.0/14.9
Wang 2012[56]	57.8/60.9	65.6/62.7	65.9/58.0	34.5/30.3	41.3/44.4	36.0/34.6
Witassek 2014[57]	61.4/66.0	76.8/50.5	65.8/50.6	54.6/38.8	43.3/53.4	25.8/10.0
Diabetic group	E/C	E/C	E/C	E/C	E/C	E/C
Abizaid 1998[58]	63.0/61.0	56.6/73.3	70.4/54.2	62.0/69.1	48.8/49.1	100.0/0.0
Akin 2010[59]	66.7/64.4	71.6/76.5	92.5/79.9	82.6/79.9	17.9/24.5	100.0/0.0

Studies	Age	Men	HT	Ds	Cs	DM
Antoniucci 2004[60]	68.5/64.0	69.0/78.0	41.5/36.0	30.0/36.0	23.0/39.0	100.0/0.0
Banning 2010[61]	65.4/65.0	71.0/79.9	–	81.5/76.7	15.8/21.7	100.0/0.0
Billinger 2008[62]	–	70.7/78.8	80.7/56.7	60.8/58.5	20.2/40.0	100.0/0.0
Blondal 2012[63]	67.2/67.5	52.2/66.8	86.2/69.2	66.1/68.5	18.7/29.2	100.0/0.0
Claessen 2011[64]	61.9/61.3	87.2/82.5	70.6/56.5	75.0/61.2	33.0/24.5	100.0/0.0
Daemen 2008[65]	64.5/62.1	66.7/80.1	79.9/62.7	74.1/74.0	11.9/21.9	100.0/0.0
Elezi 1998[66]	66.7/62.5	68.1/79.1	75.0/63.0	39.0/37.1	23.8/35.5	100.0/0.0
Fernandez 2011[67]	71.7/68.7	70.2/80.3	78.0/68.9	51.8/50.8	38.3/44.6	100.0/0.0
Garg 2008[68]	65.6/64.3	62.6/70.0	87.2/70.2	84.4/71.9	15.6/22.9	100.0/0.0
El Ghannudi 2011[69]	63.9/65.6	–	75.5/41.8	63.3/45.2	38.3/52.7	100.0/0.0
Harjai 2003[70]	64.0/60.0	63.0/75.0	63.0/43.0	8.80/4.60	28.0/43.0	100.0/0.0
Hasdai 2000[71]	64.8/62.2	66.7/79.1	56.5/35.8	36.2/35.1	31.8/45.6	100.0/0.0
Hermillier 2005[72]	62.2/62.6	63.5/74.8	81.1/64.0	71.5/67.4	–	100.0/0.0
Jain 2015[73]	65.3/62.3	69.3/80.2	78.6/63.7	67.7/60.8	17.0/25.4	100.0/0.0
Jensen 2010[74]	–	68.1/72.8	61.0/39.7	61.4/47.7	30.8/41.5	100.0/0.0
Jensen 2012[75]	63.6/64.3	74.4/75.8	76.9/51.6	85.3/68.7	26.0/30.4	100.0/0.0
Kassaian 2012[76]	59.0/57.4	53.0/75.8	61.4/46.1	78.7/61.5	26.4/47.0	100.0/0.0
Kedhi 2014[77]	63.1/63.2	63.6/64.6	82.7/82.9	78.3/78.7	24.0/29.5	100.0/0.0
Kereiakes 2010[78]	63.3/63.3	63.3/70.0	87.0/71.9	82.5/72.6	18.3/24.0	100.0/0.0
Kip 1996[79]	59.8/57.2	61.6/76.5	63.4/42.9	36.2/33.9	21.2/29.9	100.0/0.0
Kirtane 2008[80]	63.0/62.1	64.7/75.0	82.1/64.5	74.0/69.6	18.4/24.9	100.0/0.0
Kirtane 2009[81]	64.0/63.3	60.4/71.0	90.6/76.7	87.1/81.4	54.1/64.8	100.0/0.0
Kufner 2014[82]	66.6/66.8	74.5/78.0	74.0/71.5	79.5/73.5	8.0/14.5	100.0/0.0
Kumar 2007[83]	65.0/66.0	65.0/73.0	94.0/77.0	91.0/80.0	9.0/14.0	100.0/0.0
Kuramitsu 2013[84]	70.0/69.0	76.7/73.5	84.0/74.2	65.2/72.1	26.3/24.2	100.0/0.0
Lee 2006[85]	65.0/62.0	58.4/71.1	71.0/52.9	49.2/43.1	15.6/23.9	100.0/0.0
Lee 2012[7]	67.8/61.6	59.7/78.7	60.3/43.7	5.9/4.0	46.1/68.5	100.0/0.0
Lenzen 2006[86]	66.5/63.0	69.0/74.0	69.5/59.0	74.5/79.0	20.5/26.0	100.0/0.0
Lima 2013[87]	61.0/59.0	56.0/71.0	72.0/57.0	–	17.0/37.0	100.0/0.0
Lingman 2011[8]	68.0/65.5	68.5/74.5	70.9/46.9	–	15.0/24.0	100.0/0.0
Maeng 2011[88]	66.0/64.5	71.5/74.0	72.0/49.0	80.0/66.5	29.0/32.5	100.0/0.0
Marui 2015[89]	68.3/70.3	70.0/75.0	86.0/85.0	–	25.0/24.0	100.0/0.0
Mathew 2004[90]	61.8/59.8	70.0/80.0	75.0/57.0	64.0/65.0	16.0/25.0	100.0/0.0
Mehran 2004[91]	64.5/64.0	56.5/76.0	77.0/56.0	69.0/70.0	11.5/15.0	100.0/0.0
Muhlestein 2003[92]	63.0/61.0	65.0/80.0	68.0/55.0	55.0/53.0	18.0/29.0	100.0/0.0
Muramatsu 2014[93]	61.6/61.9	73.5/73.7	75.0/61.4	67.6/63.6	19.9/21.0	100.0/0.0
Norhammar 2004[94]	66.0/64.0	72.0/69.0	49.0/28.0	–	19.0/32.0	100.0/0.0
Onuma 2011[95]	64.0/61.0	70.0/79.0	72.0/51.5	64.5/66.5	16.5/26.0	100.0/0.0
Overgaard 2013[96]	60.0/58.0	68.5/80.5	68.5/43.5	57.2/50.5	28.4/41.8	100.0/0.0
Park 2009[97]	62.7/59.7	63.9/73.0	61.6/46.4	–	23.2/31.3	100.0/0.0
Silber 2013[98]	65.2/63.5	66.4/74.4	87.6/73.1	86.2/76.0	18.2/22.1	100.0/0.0
Sohrabi 2011[99]	58.1/58.2	64.7/80.6	58.8/38.0	38.2/29.5	20.6/36.4	100.0/0.0
Stein 1995[100]	60.0/58.0	62.0/75.3	61.1/41.1	–	–	100.0/0.0
Stone 2011[101]	63.0/63.8	71.3/63.2	62.5/83.1	64.0/79.4	27.1/19.6	100.0/0.0
Syed 2010[102]	63.6/61.0	57.1/70.9	92.5/76.2	89.9/79.1	24.2/38.7	100.0/0.0
Tada 2011[103]	67.3/68.8	71.5/76.0	77.0/73.0	–	18.5/20.0	100.0/0.0
Weber 2008[104]	66.6/63.2	69.3/76.8	90.4/78.3	89.6/87.1	–	100.0/0.0
Wilson 2004[105]	63.6/63.4	57.0/73.0	78.0/67.0	–	8.80/15.0	100.0/0.0
Witzenbichler 2011[106]	64.5/59.6	73.4/77.2	72.3/49.8	60.3/39.7	56.8/64.9	100.0/0.0

C = control/low risk group, Cs = current smoker, DM = diabetes mellitus, Ds = dyslipidemia, E = experimental/high risk group, HT = hypertension.

* Late nonsmokers have been included in the same category as smokers; 100% smokers have been considered.

Result of the Main Analysis

Results from this meta-analysis showed that during the in-hospital follow-up, mortality in the hypertensive and DM patients were significantly higher with RR 1.43; 95% CI: (1.05–1.94); $P = 0.02$ and RR 1.86; 95% CI: (1.68–2.06); $P < 0.00001$, respectively. The in-hospital mortality for the patients with dyslipidemia did not reach statistical significance RR 1.39; 95% CI: (0.32–5.94); $P = 0.66$. However, surprizingly, the in-hospital mortality significantly favored patients with high BMI with RR 0.61; 95% CI: (0.58–0.64); $P < 0.00001$.

Short-term mortality was significantly higher in the DM group with RR 2.11; 95% CI: (1.91–2.33); $P < 0.00001$. The result was not significant in the hypertensive group with RR 1.40; 95% CI: (0.95–2.06); $P = 0.09$; dyslipidemia group with

TABLE 4. Summarizes the Results of This Meta-Analysis

Risk Factors	In-Hospital Mortality		Short-Term Mortality		Long-Term Mortality	
	RR	*P* Value	RR	*P* Value	RR	*P* Value
Hypertension	1.43	0.02	1.40	0.09	1.45	0.00001
Dyslipidemia	1.39	0.66	0.91	0.77	1.21	0.27
Diabetes mellitus	1.86	0.00001	2.11	0.00001	1.85	0.00001
High BMI	0.61	0.00001	0.67	0.002	0.64	0.00001
Smoking	–	–	0.53	0.00001	0.49	0.00001
MS	–	–	1.05	0.61	1.29	0.0009

RR = risk ratio.

RR 0.91; 95% CI: (0.47–1.76); $P = 0.77$ and MS group with RR 1.05; 95% CI: (0.88–1.25); $P = 0.61$. Unexpectedly, the short-term mortality significantly favored the smokers and high BMI groups with RR 0.53; 95% CI: (0.45–0.62); $P < 0.00001$ and 0.67; 95% CI: (0.52–0.86); $P = 0.002$, respectively.

Long-term mortality was significantly higher in the DM, hypertensive, and MS groups with RR 1.85; 95% CI: (1.66–2.06); $P < 0.00001$, 1.45, 95% CI: (1.24–1.69); $P < 0.00001$, and 1.29; 95% CI: (1.11–1.51); $P = 0.0009$, respectively. The result for dyslipidemia was still not significant. However, the long-term mortality still significantly favored the smokers and high BMI patients with RR 0.49; 95% CI: (0.39–0.63); $P < 0.00001$ and 0.64; 95% CI: (0.54–0.75), $P < 0.00001$, respectively. The mortality risks within these subgroups have been summarized in Table 4, and the detailed results for mortality among these different subgroups have been shown in Figures 2–7.

For all of the above analyses, sensitivity analyses yielded consistent results. Based on a visual inspection of the funnel plots, there has been no evidence of publication bias for the included studies that assessed the subgroup mortality risk. Figure 8 shows the corresponding funnel plots.

DISCUSSION

Among these 844,190 patients who participated in this meta-analysis, an unexpected result has been obtained in certain subgroups of patients. A significantly higher mortality risk has been observed among the DM patients. A significantly higher in-hospital and long-term mortality risks have also been

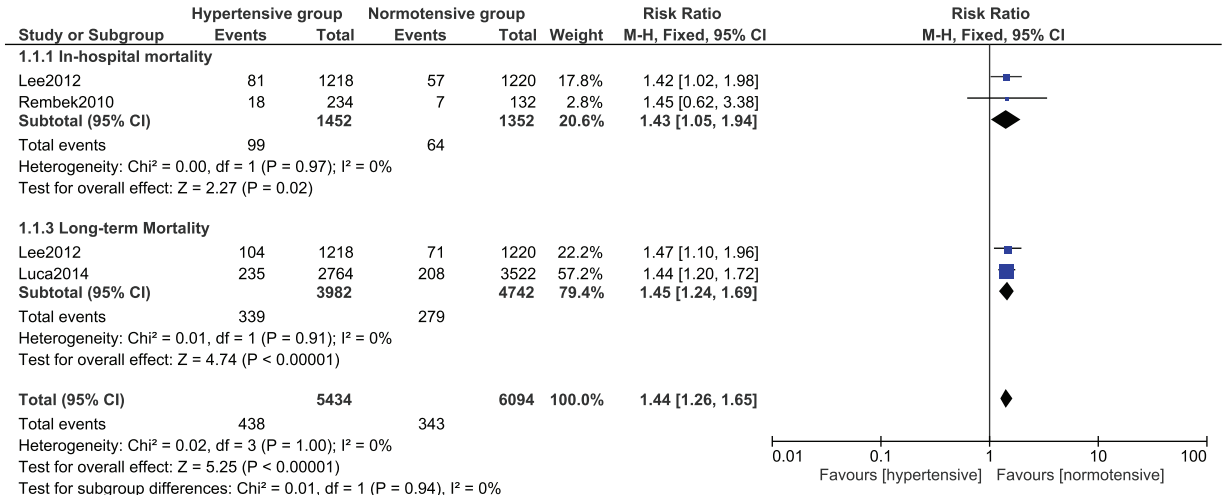


FIGURE 2. (A) Forest plot showing the in-hospital and long-term mortality risk in Hypertensive patients. (B) Forest plot showing the short-term mortality risk in hypertensive patients.

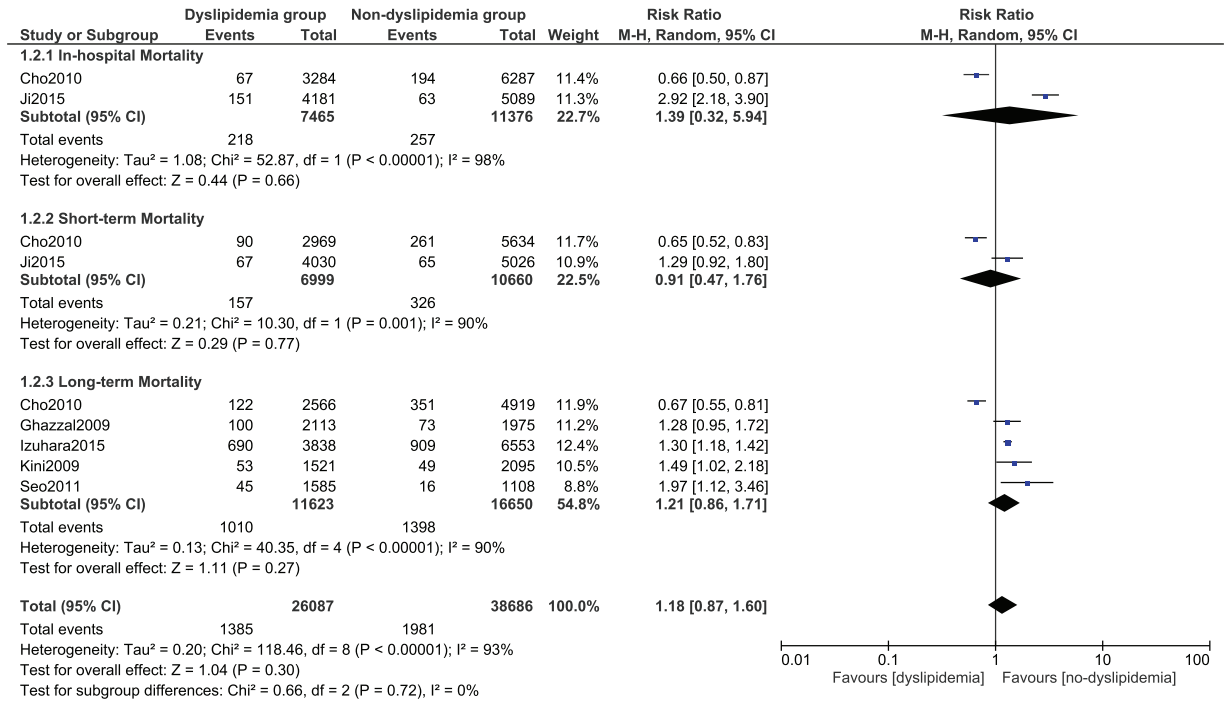


FIGURE 3. Forest plot showing the mortality in dyslipidemia patients.

observed among the hypertensive patients. Moreover, a significantly higher long-term mortality has been observed in patients with MS whereas an almost similar mortality rate has been observed in patients with and without dyslipidemia.

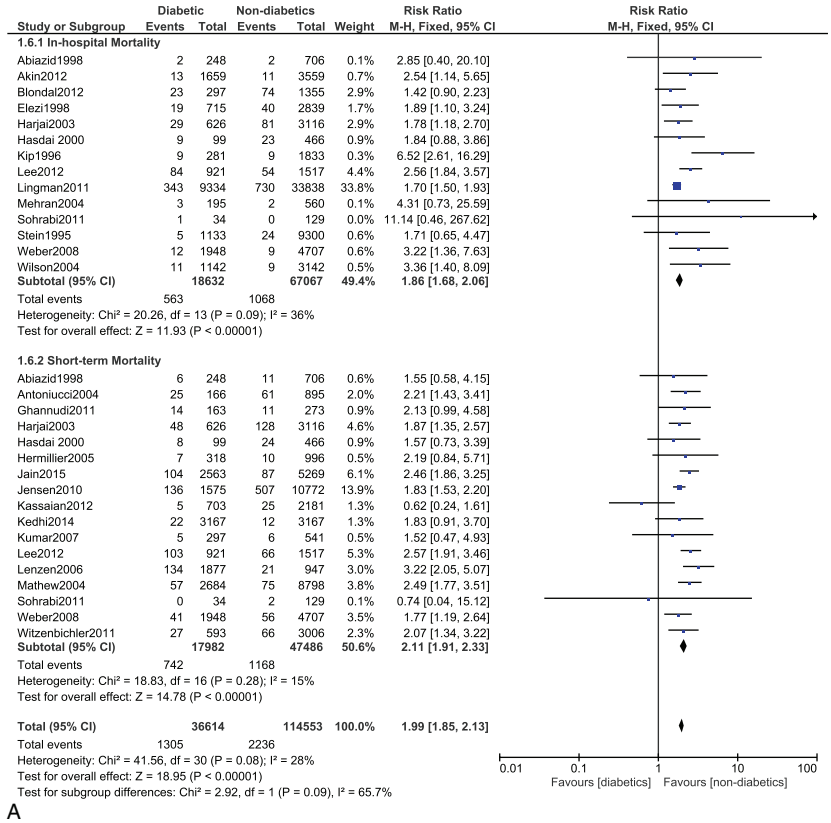
However, smokers and those patients with high BMI had an unexpectedly lower short and long-term mortality risk compared to non-smokers and low-BMI/normal weight patients, respectively, after PCI. Several possible reasons could be responsible for such an outcome.

DM is associated with a higher risk of mortality after PCI.[59] A total of 3.02%, 4.12%, and 9.24% in-hospital, short-, and long-term deaths, respectively, occurred in these DM patients compared to 1.59%, 2.46%, and 5.35% in-hospital, short-, and long-term deaths in nondiabetics patients in our study. These patients have worse adverse clinical outcomes including mortality due to severe stent thrombosis, stroke, silent myocardial infarction, or other major adverse cardiac effects. Conditions such as multicoronary vessel diseases and chronic total occlusion which are associated with DM patients partly contribute to these worse clinical outcomes after PCI. The risk of restenosis after stent implantation is also higher in diabetic patients. DM patients also have platelet dysfunction which contribute to this expected increased risk of mortality in these patients.[107] A poor response to antiplatelet agents such as aspirin and clopidogrel after drug eluting stents implantation could be another reason for such a result.[108] The use of insulin could also be another reason for this higher mortality risk in these diabetic patients.[109] Comorbidities and severe diabetic complications are associated with these insulin-treated diabetic patients which finally result in a higher mortality in this category of patients after PCI.

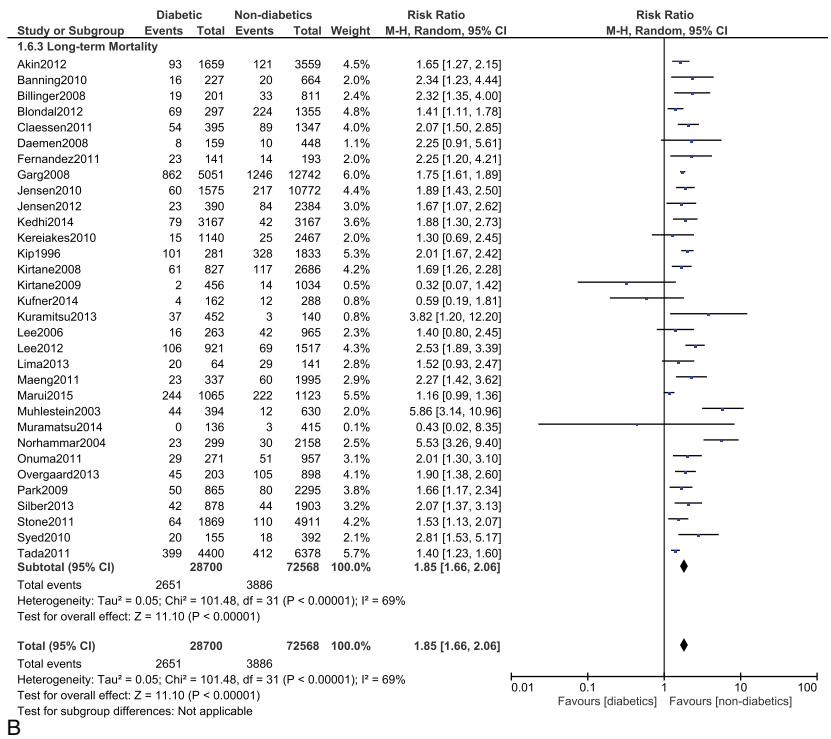
MS which is considered to be a modifiable cardiovascular risk factor, includes patients who can be obese, may have diabetes, may suffer from hypertension, and may also have dyslipidemia. The long-term mortality in these patients was significantly higher compared to those without MS after PCI. A significant increase in long-term mortality from 8.21% in non-MS to 12.1% in MS has been found in our study. Its association with comorbidities such as DM and hypertension maybe one of the reasons that lead to a higher mortality in these patients after PCI.[31]

Hypertension is another major modifiable risk factor for CAD and acute coronary syndrome. Hypertensive patients had a higher mortality risk compared to normotensive patients after PCI. A significant long-term mortality of 8.51% has been observed in the hypertensive group, compared to the normotensive group which was only 5.88% after PCI. The reasons associated with this result could be an increased in diastolic dysfunction in these hypertensive patients which could lead to severe heart failure. Moreover, by hypertension, we refer to essential hypertension which is a disease that occurs in advanced age. Other comorbid conditions such as diabetic mellitus may be present in these hypertensive patients thus, strengthening/increasing the mortality risk in these patients after PCI.[8] Patients with high blood pressure are even prone to cerebral hemorrhage if their antiplatelet dosages are not adjusted after PCI. This can also contribute to death in these patients.

Dyslipidemia is another well-known modifiable risk factor for coronary heart disease. It was expected to be associated with a higher mortality after PCI but however, the results were not significant in our study. A few studies have shown the existence of a "cholesterol paradox" whereby the mortality rate in hypercholesterolemia patients was lower compared to those with normal cholesterol levels.[20] The reasons for such a phenomenon is still not clear. However, even such a result was not evident in our study. Several factors could have been responsible for this insignificant result. The use of statin (lipid-lowering drugs) has not been studied in our meta-analysis.[110]



A



B

FIGURE 4. (A) Forest plot showing the in-hospital and short-term mortality in diabetic patients. (B) Forest plot showing the long-term mortality in diabetic patients.

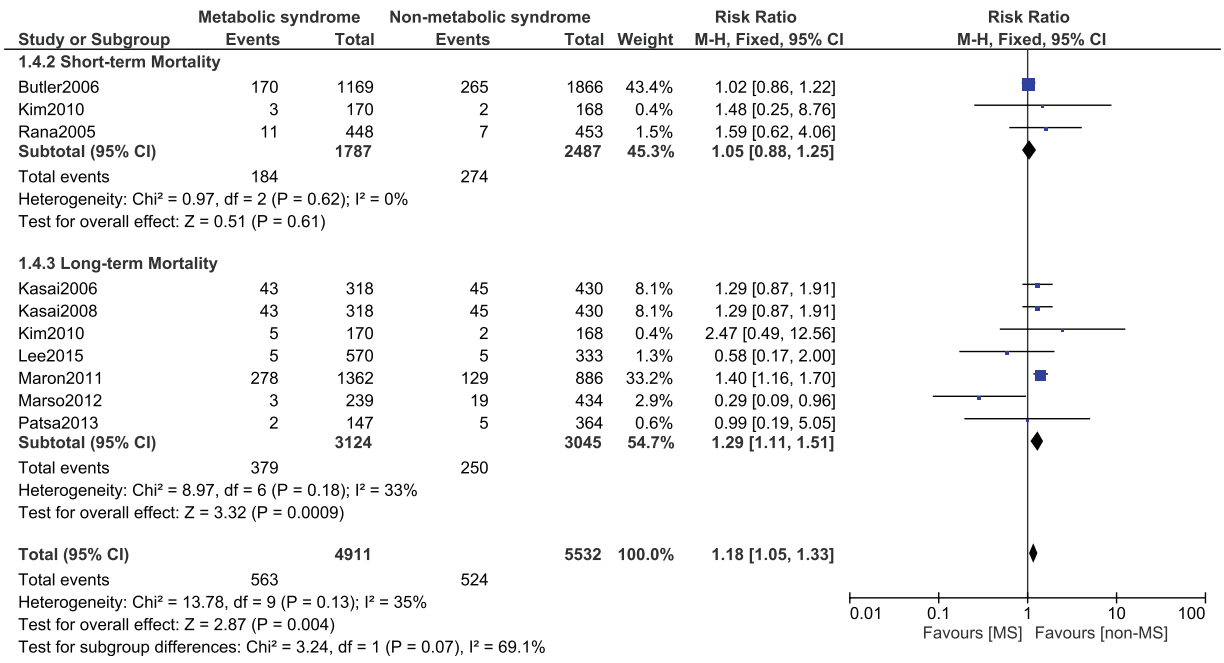
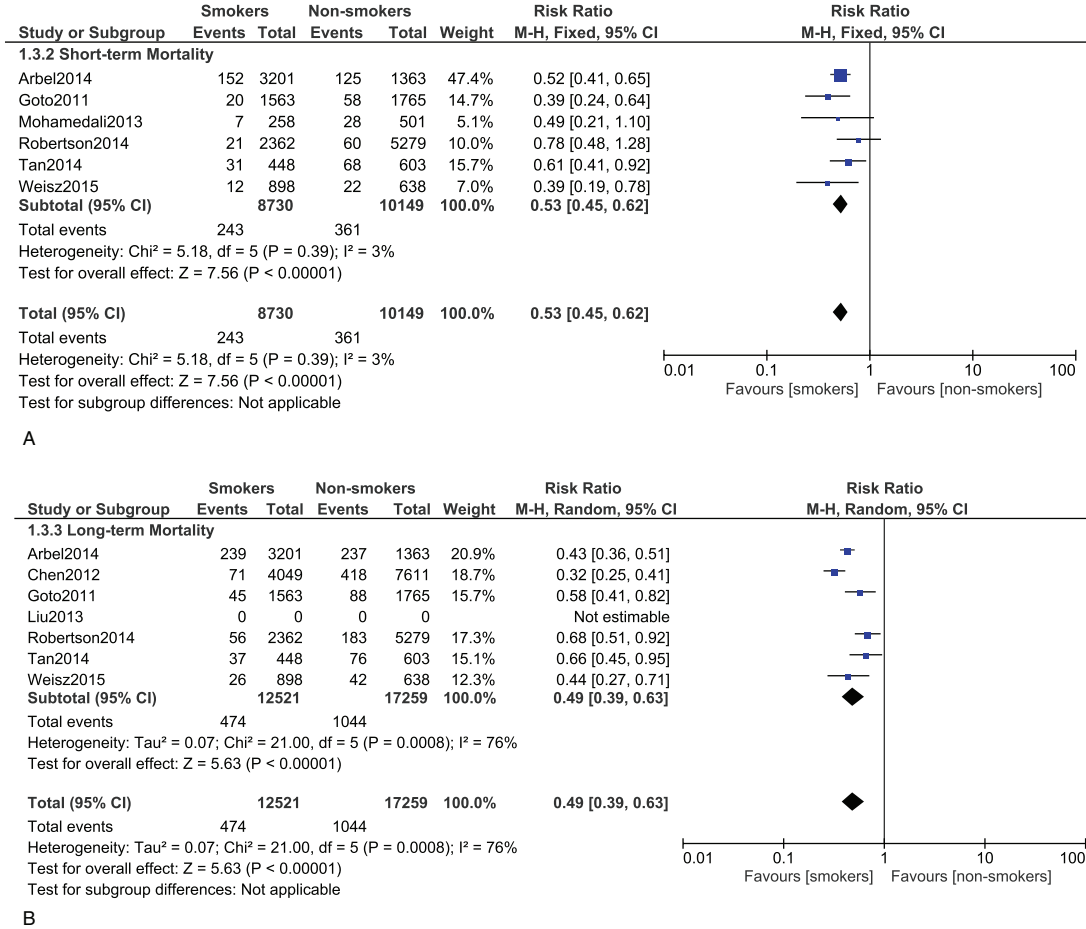


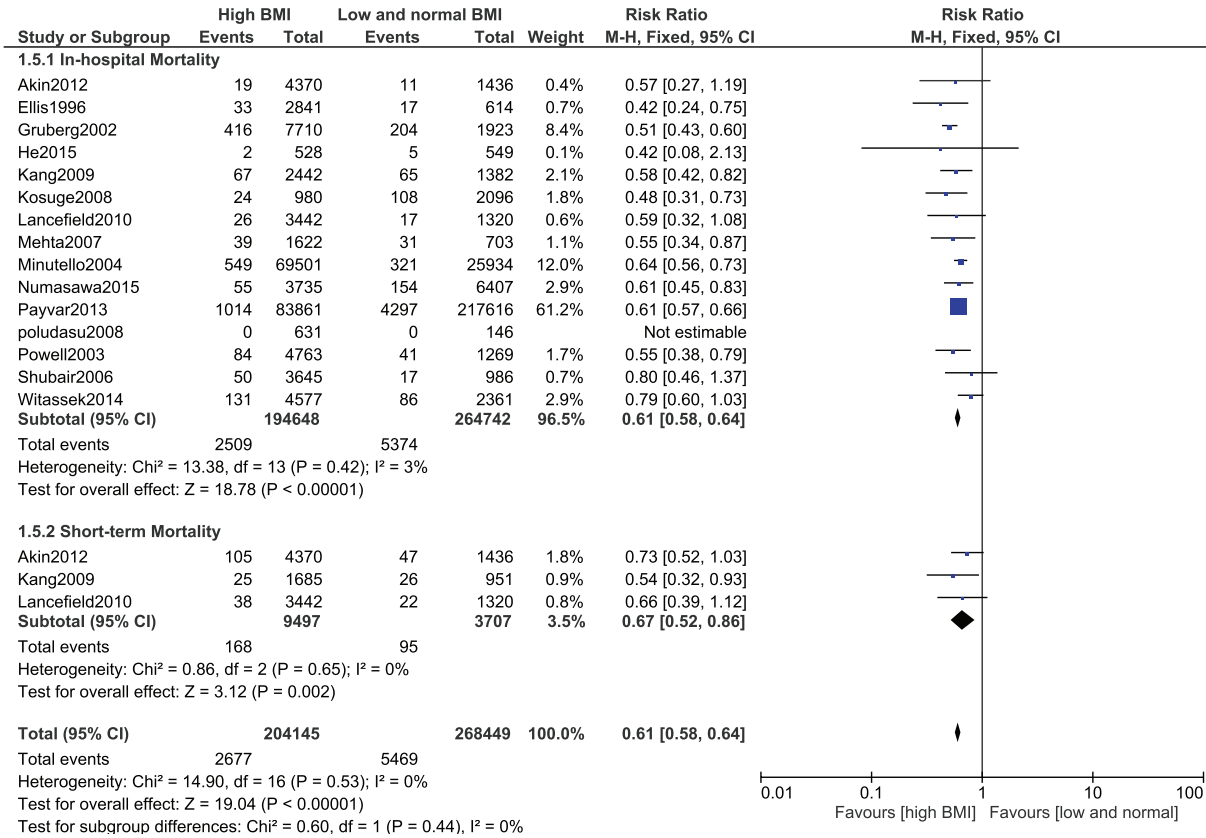
FIGURE 5. Forest plot showing the mortality in patients with metabolic syndrome.



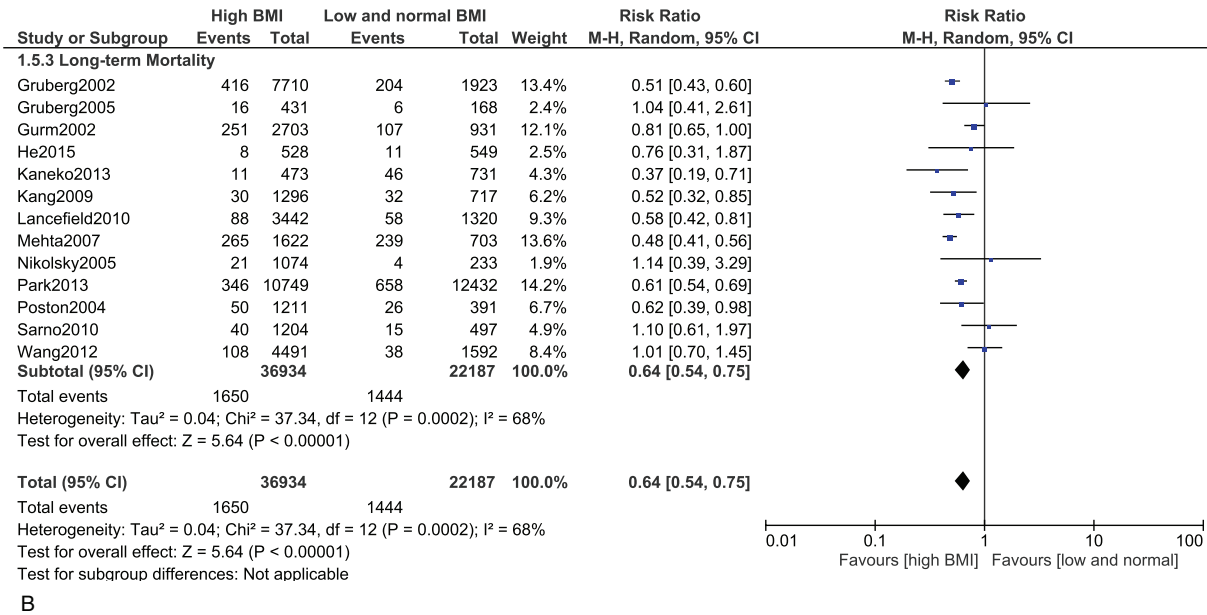
A

B

FIGURE 6. (A) Forest plot showing the short-term mortality in smokers. (B) Forest plot showing the long-term mortality in smokers.



A



B

FIGURE 7. (A) Forest plot showing the in-hospital and short-term mortality in overweight and obese patients. (B) Forest plot showing the long-term mortality in overweight and obese patients.

Obesity is another modifiable risk factor for cardiovascular diseases. Surprizingly, our study showed an unexpectedly, significantly decreased mortality in these high BMI patients in all the follow-up categories after PCI. A significant 1.79% overall death has been observed in the overweight and obese patients whereas a higher overall mortality of 2.38% was observed among the combined normal weight/underweight patients. Several studies have shown the existence of an

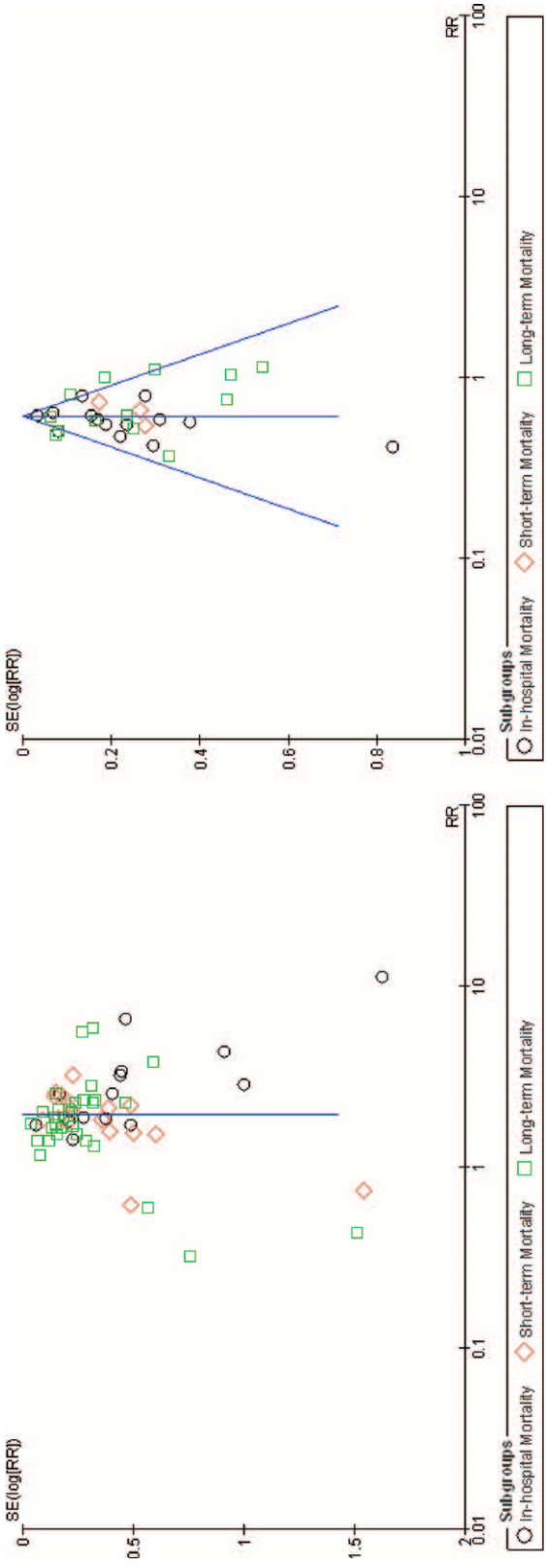


FIGURE 8. Funnel plots for the subgroup analysis.

"obesity paradox" in such patients after cardiovascular intervention.[44] The baseline features in this study showed a higher rate of diabetes, dyslipidemia, and hypertension among the overweight and obese patients. Intensive medications and aggressive medical therapies, regular counselling about health benefits, younger age, and having a good storage for nutrients after PCI could all be responsible for such a phenomenon. Size of the coronary blood vessels could also be considered as one of the reasons for this "obesity paradox."[44] However, a few studies also showed different results. The study by Akin et al[35] in 2012 revealed no evidence of such a phenomenon. In his study, normal body weight patients and obese patients had similar rates of all-cause mortality. Such a different result in his study could be due to the fact that his study dealt with the comparison of different types of drug eluting stents and their corresponding adverse clinical outcomes after PCI. However, it is not clear whether or not this increased mortality risk could also have been more prominent among the underweight which could not be compensated by the normal weight population.

Smoking, which is another modifiable cardiovascular risk factor, has proved to be associated with cardiovascular disorders. Unexpectedly, results from our study showed a significantly decreased risk of overall mortality in these smokers (3.37%) compared to nonsmokers (5.13%) after PCI. According to the baseline features in this study, most of the nonsmokers were diabetics and suffered from high blood pressure. The existence of a "smoking paradox" has also been observed in other studies. For example, the study by Hasdai and Holmes found lower adverse outcomes in smokers compared to nonsmokers after PCI.[111] The question about why smokers have a lower mortality rate compared to nonsmokers after PCI is more interesting than its answer. Reasons suggested for this smoking paradox could be younger age, a more favorable clinical and angiographic profile among these smokers, and less damage to microvascular function in these patients after PCI. However, many other studies had different results compared to our meta-analysis. The study Jang et al[112] showed that individuals who continue smoking after PCI experienced significantly poorer outcomes compared to patients who have never smoked. Another study by Castela et al showed a higher rate of vascular complications, but a similar mortality rate between smokers and nonsmokers at 1 year. However, a smaller population size and a different definition of smoker could be responsible for this different result in his study.

Apart from these cardiovascular risk factors, an increased mortality in these patients after PCI could also have been due to factors such as drug eluting stents, which are associated with a higher long-term risk of stent thrombosis. Also, glucose-lowering drugs in DM patients have been associated with an increased risk of mortality in this modifiable cardiovascular risk group.[113,114] Moreover, a study by Yusuf et al[115] showed no difference in cardiovascular mortality even with intensive lifestyle intervention in DM patients indicating that there may be other factors such as socio-economic status which contribute to this increase in mortality in these high risk patients.

This meta-analysis with a large number of patients is the one and only meta-analysis comparing mortality between patients with low and high modifiable cardiovascular risk factors after PCI. Including 100 studies consisting of 844,190 patients with several modifiable cardiovascular risk factors such as DM, high BMI, hypertension, dyslipidemia, smoking and MS, and their impact on mortality after PCI makes this meta-analysis a completely new research in the field of interventional cardiology.

Several limitations in this meta-analysis were as follows: in a few studies, all-cause mortality was not among the clinical endpoints, however, being part of it, data concerning cardiac death has been considered. One study included mortality and myocardial infarction together. Because these data could not be separated, we have included them together in our meta-analysis. One study about smokers and PCI included data for the smokers undergoing fibrinolysis and PCI together. This may affect the result of our study to a certain extent. Moreover, in 1 study, overweight patients and obese patients were classified as a BMI >23.5 and $27.5\,kg/m^2$ instead of 25 and $30\,kg/m^2$, respectively. Another study classified a BMI of $25–35\,kg/m^2$ to be considered as overweight and $>35\,kg/m^2$ to be considered as obese patients. Data for the baseline characteristics in several studies were not provided in the original article or could not be converted to dichotomous variables. Therefore, these data have been omitted in our meta-analysis. The baseline features of all the 100 studies have been analyzed and, the data concerning the number of patients with their corresponding risk factor in the whole study were obtained from the baseline features of each study. However, studies without dichotomous data at baseline, or if corresponding data were not available, have been omitted from this count. Therefore, except for the data being analyzed, the count for "modifiable cardiovascular risk factors for the whole study" is just an approximation for this study. However, despite these limitations, our data point to the urgent need for comprehensive comparison between these 2 groups of patients.

CONCLUSION

Certain modifiable cardiovascular risk subgroups had a significantly higher impact on mortality after PCI. However, mortality among the obese patients and the smokers showed an unexpected paradox after coronary intervention.

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