How common are myeloproliferative neoplasms? A systematic review and meta-analysis

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Myeloproliferative neoplasms (MPNs) are a heterogeneous group of diseases including polycythemia vera (PV), essential thrombocythemia (ET), and primary(idiopathic) myelofibrosis (PMF). In this systematic review, we provide a comprehensive report on the incidence and prevalence of MPNs across the globe. Electronic databases (PubMed, EMBASE, MEDLINE, and Web of Science) were searched from their inception to August 2012 for articles reporting MPN incidence or prevalence rates. A random effects meta-analysis was undertaken to produce combined incidence rates for PV, ET, and PMF. Both heterogeneity and small study bias were assessed. Thirty-four studies were included. Reported annual incidence rates ranged from 0.01 to 2.61, 0.21 to 2.27, and 0.22 to 0.99 per 100,000 for PV, ET, and PMF, respectively. The combined annual incidence rates for PV, ET, and PMF were 0.84, 1.03, and 0.47 per 100,000. There was high heterogeneity across disease entities ($I^2$ 97.1–99.8%) and evidence of publication bias for ET and PMF (Egger test, $P = 0.007$ and $P < 0.001$, respectively). The pooled incidence reflects the rarity of MPNs. The calculated pooled incidence rates do not reflect MPN incidence across the globe due to the high unexplained heterogeneity. Improved, widespread registration of MPNs would provide better information for global comparison of the incidence and prevalence of MPNs.

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Introduction

Myeloproliferative neoplasms (MPNs) are a rare, heterogeneous group of hematological disorders with shared biology [1], whereby abnormalities in hematopoietic stem cells transform myeloid progenitor cells leading to an overproduction of both mature and immature cells in one or more cell types of the myeloid lineage. The classic MPN entities include polycythemia vera (PV), essential thrombocythemia (ET), and primary (idiopathic) myelofibrosis (PMF). Signs and symptoms differ but include fatigue, excessive sweating, headaches, bruising, and bleeding [2–4]. Thrombotic and hemorrhagic events are the most common complications which contribute to significant morbidity and mortality [5,6]. In addition, MPN patients can spontaneously transform into either myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), also known as blast phase myelofibrosis (BF-MF) with much poorer prognosis [7–10]. Although medical, familial, and environmental risk factors have been suggested [11], to date, little is known about the etiologic mechanisms of these disease entities.

In 2001, the World Health Organization (WHO) classified the classic MPNs as neoplastic due to their clonality with additional revisions in 2008 [1,12,13]. Prior to 2001, MPNs were categorized along with chronic myeloid leukemia (CML), chronic neutrophilic leukemia, hypereosinophilic syndrome, and chronic myeloproliferative disease, unclassifiable [12–14] under the broad category of chronic myeloproliferative disorders (CMPDs) [12,15]. CML, unlike PV, ET, and PMF, has since been genetically classified as Philadelphia chromosome positive and regarded as a distinct disease entity [13]. CML has an incidence of 1.6 per 100,000 in the USA [16].

In 2005, diagnosis and treatment of Philadelphia chromosome negative MPNs were revolutionized by the discovery of the Janus Kinase 2 (JAK2) V617F mutation [17]. Approximately 95% of PV patients have the JAK2V617F mutation as do approximately 50% of ET and PMF patients [18]. More recently, new mutations in the endoplasmic reticulum chaperone, CALR have been discovered in patients who are both JAK2 and MPL negative [19,20]. Additional mutations have been identified that contribute to disease pathogenesis, progression and prognosis including JAK2 exon 12, LNK, TET2, MPL, CBL, and EZH2 [,16,18–25].

Using a systematic approach we aimed to identify, collate, and produce overall estimates of incidence and prevalence rates for MPNs and CMPDs assessing variability by gender, region, and time period.

Additional Supporting Information may be found in the online version of this article.

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Methods

A detailed, systematic search of the literature was conducted using PubMed (US National Library of Medicine and the National Institutes of Health), Ovid MEDLINE (US National Library of Medicine), EMBASE (Elsevier Biomedical and Pharmacological Database) and Web of Science (Thomas Reuters Online Academic Citation Index) with publication dates ranging from 1946 to August 2012. To ensure an extensive range of publications were identified, broad search terms for classic MPNs, including PV, ET, and PMF, and epidemiological variables (e.g., incidence, prevalence, frequency) were utilized with the addition of alternative spellings and umbrella terms, e.g., myeloid metaplasia and erythremia. Search terms were limited to classic MPNs and did not include terms for CML since this was considered a distinct disease entity. Hematological malignancies such as leukemia were not searched therefore potentially overlooking some manuscripts. No language, time frame or other restrictions were enforced. Abstracts not in English were translated using Google Translate to ensure studies were not missed. Four studies included in this report were published in Spanish, French, Japanese, and Finnish and translated to English using Google Translate. The inclusion criteria required reports to include primary incidence and/or prevalence data. Reports were excluded if they were abstract only, unavailable and did not report information or details of the source population or were case series from a single centre.

Duplicate articles were identified and removed. Title and abstract screening was undertaken independently by four researchers (GJT, LAA, SH, MOR). Independent full text review was undertaken by GJT and LAA. The references in each included article were checked to identify additional articles not found by the database searches.

To obtain additional, relevant incidence and prevalence data that had not been included in reports, corresponding authors (n = 12) were contacted to provide additional data. Communication was successful for 6 [25–30] reports, contact details were no longer applicable for 1 [31] corresponding author, 1 [32] author had retired and 4 [33–36] were unresponsive.

Statistical analysis

Using a DerSimonian and Laird random effects model [37–39] pooled incidence rates and 95% confidence intervals were calculated for each disease entity overall and stratified by time period, region and sex. Principally, pooled incidence rates for crude data were obtained. Studies reporting incidence rates only were included in reports. Heterogeneity between studies was calculated using the I² test. Pooled incidence rates were only obtained for studies published before 2005, the date when the JAK2V617F and Exon 12 mutations were discovered. Pooled incidence rates could not be used as a comparison with the pooled incidence rate. Subsequently, studies reporting crude and additional adjusted incidence rates were obtained. Heterogeneity between studies was calculated using the I² test. Pooled incidence rates were only obtained for studies published before 2005, the date when the JAK2V617F and Exon 12 mutations were discovered. Pooled incidence rates could not be determined for PV and ET because of a lack of studies distinguishing date pre and post 2005 (n = 1 [28]). Sensitivity analyses were conducted using step-wise study removal to assess which study had the most impact on I² and P for heterogeneity. Meta-regression was utilized to determine whether there were any difference in incidence rates evident between geographical regions [Europe (Including Israel), North America and Australasia]. Small study bias was assessed using Begg and Mazumdar’s ranked correlation test and Egger’s linear regression test, producing Begg’s funnel plots and 95% confidence intervals.

For all statistical tests a P < 0.05 was considered statistically significant. The limited number of studies reporting prevalence of the classic MPNs was insufficient to warrant meta-analysis. Statistical analyses were performed using STATA 12.0 (StataCorp, College Station, TX) [40].

Results

A total of 4,609 articles (Pubmed-700, EMBASE-2,898, Web of Science-448, and MEDLINE-563) were initially identified (Fig. 1). Duplicates were identified and removed (n = 328) leaving 4,281 articles for title and abstract review. From these, 233 full text articles were reviewed and 27 articles met the inclusion criteria. A total of 4,582 articles were excluded not meeting the inclusion criteria. The full reference search identified a further 7 [27,41–46] articles, 3 [41,45,46] of which were obtained through author correspondence. In total, we included 34 reports with incidence data from 1935 to 2010 (Supporting Information 1–3) and 8 reports with prevalence data from 1950 to 2013 (Table II). The majority of incidence data (n = 24) and additional references originated in European and North American populations. Pooled incidence rates were calculated for classic MPNs, PV, ET, and PMF. A total of 11 reports with incidence and prevalence data for CMPDs combined were included.

Incidence: Polycythemia vera (PV)

Twenty studies were included in the crude PV analysis comprising populations from Europe (n = 14), North America (n = 4), Asia (n = 1), and Australasia (n = 1). The crude annual incidence rates ranged from 0.01 [47] to 2.61 [48] per 100,000 (people/population) with a pooled annual incidence rate of 0.67 per 100,000 (95% CI: 0.47–0.96) (Fig. 2a). Sensitivity analysis indicated that Kurita’s study [47] (Asia) had most influence on the overall pooled incidence rate. Removal of Kurita’s study produced a pooled annual incidence rate of 0.84 per 100,000 (95% CI: 0.70–1.01) (Table I). This rate will be used in the subsequent discussion because the methodology used in Kurita’s study is likely to have substantially underestimated the incidence of PV in Japan because of a lack of accurate coverage across the country. No evidence of small study bias (which might be due to publication bias or other associations between the size of studies and the incidence that may have influenced its availability) was detected (Table I). Pooled annual incidence from studies before 2005 remained at 0.84 per 100,000 due to insufficient data to examine incidence after 2005 (n = 1 [28]) (Table I). Meta-analysis of European data revealed an incidence rate of 1.05 per 100,000 (95% CI: 1.03–1.07) compared
to 0.94 per 100,000 (95% CI: 0.92–0.96) in North America. Due to the limited number of studies from Asia (n = 1 [47]) and Australasia (n = 1 [49]), pooled incidence rates were not calculated for these regions. No interaction by geographical location for PV was identified, \( P = 0.813 \) (Table I). Crude annual incidence did not significantly differ between males (0.64 per 100,000, 95% CI: 0.28–1.45) and females (0.51 per 100,000, 95% CI: 0.21–1.23) within the studies (n = 10 [25,28,44,48,50–55]) reporting incidence by gender. Excluding Kurita’s study, crude annual incidence did not significantly differ between males (0.87 per 100,000, 95% CI: 0.58–1.30) and females (0.73 per 100,000, 95% CI: 0.46–1.15), \( P = 0.634 \) (Table I). Similar to the pooled annual incidence rate, this rate will be used in the subsequent discussion due to methodology used in Kurita’s study. Crude and adjusted annual incidence rates excluding Kurita’s study resulted in a pooled annual incidence rate of 0.91 per 100,000 (95% CI: 0.75–1.09).

### Incidence: Essential thrombocytemia (ET)

Ten studies reported crude incidence of ET and were limited to Europe (n = 8) and North America (n = 2). The crude annual incidence ranged from 0.21 [35] to 2.53 [29] per 100,000 with an annual pooled incidence rate of 1.03 per 100,000 (95% CI: 0.58–1.80) (Fig. 2b). The Chaiter et al. [35] study from Israel had most influence on the overall pooled incidence rate. A sensitivity analysis which removed this study from the analysis produced an annual incidence rate of 1.22 per 100,000 (95% CI: 0.68–2.17). There was evidence of small study bias (Egger’s test, \( P = 0.007 \) (Table I). The pooled annual incidence rate of ET was 1.03 per 100,000 (95% CI: 0.58–1.80) (Fig. 2b).
Incidence rate for studies from before 2005 was 1.01 per 100,000 (95% CI: 0.58–1.75) (Table I), with insufficient data to examine incidence after 2005 (n = 1 [28]). Analysis of data by geographic region produced a pooled annual incidence rate of 1.60 per 100,000 in Europe (95% CI: 1.53–1.68) compared to 0.96 per 100,000 (95% CI: 0.27–3.35) in North America. No interaction by geographical location for ET was identified, P = 0.909 (Table I). Pooled annual incidence was higher in males (1.44 per 100,000, 95% CI: 0.81–2.53) than females (2.12 per 100,000, 95% CI: 1.27–3.54) though P value for interaction did not reach statistical significance, P = 0.549 (Table I). When adjusted and crude annual rates combined were incorporated into the meta-analysis a pooled annual incidence rate of 0.96 per 100,000 was obtained (95% CI: 0.59–1.56).

### Incidence: Primary myelofibrosis (PMF)

Twelve studies reported crude incidence of PMF from Europe (n = 8), North America (n = 2), and Australasia (n = 2). The crude annual incidence rates ranged from 0.22 [30] to 0.99 [56] per 100,000 with a pooled annual rate of 0.47 per 100,000 (95% CI: 0.34–0.65) (Fig. 2c). Rollison et al. [30] had the most influence on the overall pooled incidence rate. A sensitivity analysis which removed this study produced an annual pooled incidence rate of 0.50 (95% CI: 0.41–0.62). There was evidence of small study bias indicated by Egger’s linear regression test, P ≤ 0.001 (Table I). Analysis of studies before 2005 showed no significant difference (0.49 per 100,000, 95% CI 0.34–0.70) compared to the overall annual incidence rate (Table I). There was insufficient data to examine incidence after 2005 (n = 1 [28]). The pooled annual incidence rate by geographic region was 0.46 per 100,000 (95% CI: 0.42–0.49) for Europe, 0.46 per 100,000 (95% CI: 0.11–2.01) for North America and 0.63 per 100,000 (95% CI: 0.40–0.98) for Australasia. No significant difference between geographic regions was observed, P = 0.435 (Table I). The annual incidence rate for males (0.59 per 100,000, 95% CI: 0.39–0.90) was slightly higher than for females (0.30 per 100,000, 95% CI: 0.22–0.42), P = 0.052 (Table I).

### Incidence: Classsic MPNs combined

Nine studies reported incidence for classic MPNs combined and where limited to Europe (n = 8) and North America (n = 1). The crude annual incidence rate ranged from 1.15 [27] to 4.99 [48] per 100,000 with a pooled annual incidence rate of 2.58 per 100,000 (95% CI: 1.90–3.50) (Table I). Broccia et al. [27] had the most influence on the overall pooled incidence rate and a sensitivity analysis excluding this study gave a combined annual incidence rate of 2.85 per 100,000 (95% CI: 2.06–3.95). There was evidence of small study bias (Egger’s test, P = 0.039) (Table I). Pooled annual incidence before 2005 did not differ (2.52 per 100,000, 95% CI 1.91–3.33) compared to the overall reported incidence rate (Table I). There was insufficient data to examine incidence after 2005 (n = 1 [28]). The crude pooled annual incidence for Europe was 2.51 per 100,000 (95% CI: 2.45–2.57), but limited studies (n = 1 [30]) restricted further meta-analysis by region. No significant difference between geographic regions was observed, P = 0.452 (Table I). Annual incidence rates did not differ significantly between males (2.56 per 100,000, 95% CI: 1.12–5.81) and females (2.27 per 100,000, 95% CI: 0.95–5.42), P = 0.959 (Table I). No studies reported overall adjusted rates for classic MPNs combined.

### Pediatric incidence

Pediatric (age range 0–16 years) annual incidence data was published in 4 [33,34,43,57] included studies, but no data were reported for pediatric PV. Pediatric annual incidence of ET ranged between
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**TABLE II. Prevalence Studies Included in Systematic Review**

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Area</th>
<th>Case identification source</th>
<th>No. of cases</th>
<th>Case identification source</th>
<th>No. of cases</th>
<th>Region</th>
<th>No. of cases</th>
<th>Case identification source</th>
<th>No. of cases</th>
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</thead>
<tbody>
<tr>
<td>1951–1960</td>
<td>USA</td>
<td>2–North America</td>
<td>PV (City)—60, PMF (City)—60</td>
<td>ET—66</td>
<td>1–Europe</td>
<td></td>
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<tr>
<td>1951–1960</td>
<td>Australia</td>
<td>4–Australia</td>
<td>PV (Metro)—73, PMF (Metro)—50, PMF (City)—30, PMF (Metro)—30</td>
<td>ET—66</td>
<td>1–Europe</td>
<td></td>
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<tr>
<td>1950–1984</td>
<td>Sweden</td>
<td>2–North America</td>
<td>PV (City)—13, PMF (City)—13</td>
<td>ET—66</td>
<td>2–North America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Canada</td>
<td>2–North America</td>
<td>PV—Not Reported, PMF—Not Reported</td>
<td>ET—66</td>
<td>2–North America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>United Kingdom</td>
<td>1–Europe</td>
<td>ET—42.51, PMF—13.1, PV—1.76</td>
<td>ET—66</td>
<td>1–Europe</td>
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<tr>
<td></td>
<td>USA</td>
<td>2–North America</td>
<td>ET—42.51, PMF—13.1, PV—1.76</td>
<td>ET—66</td>
<td>2–North America</td>
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<tr>
<td></td>
<td>United States of America</td>
<td>2–North America</td>
<td>ET—42.51, PMF—13.1, PV—1.76</td>
<td>ET—66</td>
<td>2–North America</td>
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</table>

PMNs are uncommon across the geographical regions investigated. Meta-analysis identified ET to be the most common classic MPN (annual incidence 1.03 per 100,000) followed by PV (annual incidence 0.84 per 100,000) and PMF (annual incidence 0.47 per 100,000) (Table I). PMF incidence should be cautiously interpreted as it is unclear whether secondary myelofibrosis was included in some reported incidence rates. When pooled annual incidence by geographic region was calculated, Europe was identified to have the highest incidence for PV (1.05 per 100,000) and ET (1.60 per 100,000) while PMF was highest in Australia (0.63 per 100,000). The pooled incidence rates reported by region are comprised of a wide range of incidence rates, limited studies were available for some areas having high statistical heterogeneity. In this review Europe contributed the highest number of published studies (n = 22) compared to other geographic regions, increasing statistical power and enabling pooled incidence rates to be calculated. A recent review article investigating the incidence and prevalence of MPNs in Europe reported incidence ranges per 100,000 of 0.68 to 2.6 for PV, 0.38 to 1.7 for ET and 0.1 to 1.0 for PMF [61]. Prevalence rates per 100,000 ranged from 4.96 to 30.00 for PV, 4.00 and 24.00 for ET and 0.51 to 2.7 for PMF [61]. These are in line with the pooled incidence rates (Table I) and prevalence ranges (Table II) reported in this manuscript. The current review provides a more comprehensive report of MPNs extending the literature search to four databases and incorporating studies in all languages and time frames from across the globe. This resulted in the ascertainment of 22 European studies in contrast to the 11 included by Moulard et al. [61] and 12 studies from other regions.

The studies included in this review showed high heterogeneity, demonstrating that the reported incidence rates are unlikely to be measuring a single, true underlying value. Incidence rate variability may be explained by a number of factors. Firstly, some regions may have a true higher incidence rate due to differing etiological exposures although these remain to be elucidated [11]. Secondly, incident cases were ascertained by diagnostic criteria recommended during the time-frame of each study period ranging from as early as 1935 up to 2010. Since the discovery of JAK2 mutations in 2005 [17], diagnostic guidelines now incorporate JAK2 testing although ET and PMF may be diagnosed without the presence of JAK2 mutations. Before 2005, diagnostic guidelines were similar across study regions [28,35,47,50,51,53,62], relying solely on biological results including blood tests, morphological analysis, and bone marrow biopsies. Due to the biological similarities these diseases possess with leukemias and myelodysplastic syndromes, disease misclassification may occur, mis-estimating the true incidence of these diseases. Thirdly, owing to the chronic nature of MPNs, individuals can be asymptomatic for many years [63], particularly those with PV and ET where diagnosis can be incidental [64,65]. The reported incidence and prevalence rates are
therefore likely to underestimate the true disease rate in the general population. Fourthly, most studies in this review reported population data originating from higher income, developed countries with superior healthcare infrastructure such as Sweden [66], and the United Kingdom [67]. These countries have cancer registries, well established for many decades, allowing higher quality, more accurate reporting and record keeping of these rare malignancies. In countries with limited healthcare resources, diagnostic accuracy and registration of MPNs, particularly in the JAK2 era, where genetic testing is not feasible, may contribute to misclassification and underreporting of MPNs [68–70]. Finally, although no small study bias was detected for PV, Egger’s linear regression test suggested this bias for ET (P = 0.007) and PMF (P < 0.001) (Table I). Publication bias favoring publication of studies reporting higher incidence rates is likely.

MPNs have been reported in children [33,34,43,57] with a calculated annual incidence as low as 0.003 per 100,000 [43] reflecting the extreme rarity of these diseases in the pediatric population. The survival and prevalence of pediatric MPNs in the general population is unknown.

The incidence and prevalence rates reported in this review reflect the rarity of these diseases in the general population when compared to other cancers, notably breast and lung cancer [71] for which the annual incidence in the United Kingdom is 157 and 67.5 per 100,000 [72], respectively. The MPNs have unknown etiology and are regarded as chronic diseases contributing significantly to morbidity and mortality [5,6]. Signs and symptoms of these diseases generally do not present until later in life [63–65]. Everyday living and quality of life (QOL) are affected by symptoms including fatigue, night sweats, and pruritus [73]. Additionally, thrombotic and hemorrhagic events, such as stroke and thromboembolisms can greatly reduce one’s QOL [5,6]. Overall survival of PV and ET is respectable with a median survival of 10–16 years for PV [74] and 10–22 years for ET [74,75]. However, individuals with PMF have a much poorer median survival of 4–5 years [76], compared to PV and ET. These figures reflect the high prevalence of PV and ET compared to PMF in the general population (Table II). The prevalence of individuals living with these diseases incurs significant burden, both with cost of treatment and associated side effects. The mean annual cost for North American health services for treating someone with PV is $11,927, followed by $19,672 for ET and $34,690 for PMF [77]. Improved reporting of MPNs would facilitate planning and allocation of resources to treat these chronic conditions.

In conclusion, this review provides a comprehensive summary reporting the incidence of MPNs in the general population and meta-analysis. The calculated pooled rates however are not a true reflection of MPN incidence and cannot be accentuated across the globe due to high, unexplained heterogeneity potentially attributed to time period, geographic location, disease registration and/or diagnostic classification. Although the discovery of JAK2 in 2005 has changed the classification and diagnosis of MPNs there remains an absence of published data on the incidence of MPNs post 2005, with only 4 studies identified. The paucity of published incidence data after 2005 emphasizes the need for more epidemiological studies investigating the incidence and prevalence of these rare diseases. Furthermore, worldwide significance of MPNs is unknown due to lack of cancer registration in various regions. Establishment of cancer registration could aid accurate data on the incidence and prevalence of MPNs and other malignant diseases [68–70,78].

Author Contributions
LAA was the principal investigator and takes responsibility for the paper; GJT and MOR conducted all the statistical analysis using STATA 12 software. GJT wrote the first draft of the paper; LAA, GJT, MOR, SH were involved in the review of titles and abstracts. All authors contributed to the interpretation of the results and writing of the papers. All authors approved the final version of the article.

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