Cardiovascular Mortality and Related Risk Factors among Persons with Schizophrenia: A Review of the Published Literature

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ABSTRACT

Although persons with schizophrenia (PWS) are entitled to health care and medical preventive and curative treatments in accordance with the same standards as other persons, they suffer from excess mortality compared with the general population. The main cause of natural premature death of PWS is attributed to cardiovascular disorders (CVD). We reviewed the studies of PWS, their risk factors and CVD mortality. In every study, PWS have increased risk of CVD mortality. Additionally, most but not all of the studies found increased CVD behavioral risk factors (i.e., smoking, sedentary life style/less physical activity, increased body mass index (BMI)) in PWS. In order to promote better health care to this population, we propose general recommendations to service users and their families, general and mental health professionals and policy makers. Severe mental illness such as schizophrenia should be addressed as a "risk equivalent" for CVD. Awareness of this association should be implemented in routine psychiatric and general medicine practice as well as at national levels for policy makers. Cardiovascular morbidity and mortality should be referred to as a measure of quality of care. Better communication between different physicians and other health care providers, who treat PWS, should be encouraged. This can be accompanied with technological advances (i.e., unified electronic medical record). Understanding of suggested treatment and adherence to recommendations in PWS may be improved by if relatives and friends accompany the patient in medical settings.

Key Words: Schizophrenia, cardiovascular mortality, cardiovascular risk factors, health service

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INTRODUCTION

Persons with mental disorders are entitled to health care and medical treatments in accordance with the same standards as other persons.[1,2] However, persons with schizophrenia (PWS) suffer from excess mortality risk from both natural and un-natural (such as suicide, homicide or accidents) causes[3,4] compared with the general population. Importantly, this gap may have been growing in the last few decades.[4] The main cause of natural premature death of PWS is attributed to cardiovascular disorders (CVD).[5] Death rate attributed to CVD has declined in the past decades. Between the years 1998 to 2008, the rate of death attributable to CVD declined by 30.6 percent in the general population of the United States.[6]

Similarly, CVD risk factors show decreases over the past decades. Monitoring for risk factors between the years 1979 to 1996 across 38 populations from 21 countries in four continents, the risk factors are trending downwards in most populations.[7] However, it seems that PWS do not benefit from this risk reduction. Accordingly, the triple aim of this paper is: 1) to review the growing body of research regarding excess CVD mortality and CVD risk factors among PWS; 2) to describe possible reasons for the excess of CVD mortality (e.g., socio-economic status (SES) inequality, gaps in access to medical treatment); and 3) to suggest recommendations for service users and their families, mental and general health professionals and policy makers.

STUDY SELECTION

Methods

We conducted a search of the literature to review major factors related to CVD mortality in PWS, and the CVD risk factors. Based on findings from large cohort and case-control studies from different countries, the main modifiable risk factors—which have been known for decades—are both behavioral (e.g., smoking, sedentary lifestyle) and biological (e.g., hypertension, dyslipidemia, obesity, diabetes mellitus).[8-11] Similarly, the eight risk factors reported by the World Health Organization (alcohol use, tobacco use, high blood pressure, high body mass index (BMI), high cholesterol, high blood glucose, low fruit and vegetable intake, and physical inactivity) account for 61 percent of cardiovascular deaths.[11]

Accordingly, our search included the following terms: schizophrenia AND mortality AND (cardiovascular OR hypertension OR “metabolic

syndrome" OR diabetes OR smoking OR "sedentary life style" OR obesity OR dyslipidemia). Our inclusion criteria were: (a) publication type: epidemiological comparative cohort, case-control or cross-sectional studies; (b) published between 1 January 2006 to 1 December 2012; and (c) English language publications. We limited our literature search to this period because a comprehensive systematic-review and meta-analysis published in 2007 reviewed studies until 31 January 2006. Publications were retrieved by an extensive dataset search from PubMed that was conducted in the period from November 2012 to January 2013. Titles and abstracts were read by the authors to determine whether the publication suited the search criteria. Papers that met search criteria were accessed to review the full text. Reviews and meta-analysis were reviewed to find other relevant sources of data.

The initial search yielded 245 papers and searches within reviews gave a total of 253 papers of which 37 were relevant. Papers were excluded if they investigated other psychiatric disorders and/or failed to separate schizophrenia from other psychiatric disorders (n=11), were case reports (n=7), opinion papers (n=23) or reviews (n=58), studies of cardiac and autonomic nervous system functioning (n=13), schizophrenia treatment (n=8), all or other (non-CVD) causes of mortality (n=13), interventions studies (n=14), non-epidemiological studies and/or without comparison group (n=25) or were not relevant (n=44).

The reviewed studies were grouped into two categories: cardiovascular mortality studies (Ia) and cardiovascular risk factors studies (Ib). The studies are described in reversed order of publication (from late to early). In section II we suggest possible explanations to the findings regarding cardiovascular mortality and risk factors among PWS. Several studies are cited in more than one section as they include relevant data (Table 1 and Table 2).

I. CVD EXCESS MORTALITY AMONG PWS

Ia. Cardiovascular mortality studies (Table 1)

Wu, et al.[12] reported a case-control study that included 591 PWS after myocardial infarction (MI) in Taiwan that found the inpatient mortality of PWS was 2.7 times higher compared to controls without schizophrenia. Ratliff, et al.[13] investigated 106 obese PWS. PWS had a vascular age 14 years older than their actual age compared to obese National Health and Nutrition Examination Survey (NHANES) participants without schizophrenia, who had a seven year difference. The probability of experiencing a CVD event within the next ten years was 10.7 percent for obese PWS and 8.5 percent for

Table 1

CVD Mortality among PWS

Authors	Publication Year	Study Design (years of follow-up/ recruitment)	PWS (n)	Control Group (n)	Place	Main Findings (p-value/95% CI)
Wu, et al.[12]	2012	Case-control of MI inpatients (1996-2007)	591	Inpatients with MI without schizophrenia (300,000)	Taiwan	OR=2.68 (1.73-4.15).
Ratliff, et al.[13]	2012	Case-control (10 years)	106	Obese controls without schizophrenia from the 2005-2008 NHANES (197) matched on age, gender, race and BMI	US	The 10 years CVD event probability 10.7% *vs.* 8.5%.
Morden, et al.[14]	2012	Case-control (2000-2007)	65,362	Persons without schizophrenia (65,362), matched on age, service access year and location in the VA service.	Wales	CVD mortality rates were higher for PWS although varied across the years. In 2000: CVD death rate for PWS 81 per 100,000; for controls 64 per 100,000 (NS). In 2007: 103 per 100,000 *vs.* 84 per 100,000, respectively ($p<0.05$).
Lahti, et al.[15]	2012	Helsinki birth cohort study (30 years, years of birth – 1934-1944)	204	Total birth cohort (12,939)	Finland	HR=2.92 (1.70-5.0).
Laursen & Nordentoft[16]	2011	Population-based cohort study (1994-2006)	978	General population (4,818,168)	Denmark	MRR across follow-up period 1.12 (1.08-1.15).
Kelly, et al.[17]	2010	Retrospective cohort study (1994-2004)	1,686	Maryland general population	US	Age and sex adjusted SMR=4.02 (2.88-5.45).

Table 1 contd.

Brown, et al.[18]	2010	Prospective record linkage study (1981-2006)	370	England & Wales mortality data registry	UK	CVD SMR=2.25 (1.59-3.11); DM SMR=6.14 (1.67-15.73).
Kilbourne, et al.[19]	2009	1999 Large Health Survey of Veterans, Case-control study	22,817	Patients without psychiatric disorder (16,072)	US	CVD mortality HR=1.37 (1.26-1.49); Younger age of CVD death: PWS average age 68.6 years, without a psychiatric diagnosis 76.5 years, p<0.001.
Tokuda, et al.[20]	2008	Case-control study (1987-2004)	1,108	Admitted patients without schizophrenia (189,049)	Japan	OR=2.63 (1.20-5.77).
Fors, et al.[21]	2007	Case-control cohort study (1991-2000)	255	1,275 matched on age, sex and living area	Sweden	RR=2.4, p=0.003 in men, not in women.
Laursen, et al.[22]	2007	Register based study	17,660	Cohort population (5,500,000)	Denmark	SMR=2.07 (1.9-2.3).

BMI = Body mass index; CI = Confidence interval; CVD = Cardiovascular disease; DM = Diabetes mellitus; HR = Hazard ratio; HTN = Hypertension; MRR = Mortality rate ratio; NHANES = National Health and Nutrition Examination Survey; PWS = Persons with schizophrenia; RR = Relative risk; SMR = Standardized mortality ratio; VA = Veterans Affairs.

obese NHANES participants ($p<0.01$). Morden, et al.[14] followed 65,362 PWS from the veteran affairs health system in Wales. Compared to controls without schizophrenia, PWS had higher prevalence of diabetes mellitus (DM) and obesity. CVD and hypertension (HTN) were less often diagnosed. CVD mortality* rates were higher for PWS compared to controls without schizophrenia, and varied across the years of study: in the year 2000, the CVD death rate was 81 per 100,000 for PWS compared to 64 per 100,000 for controls without schizophrenia (a non-statistical significant difference). In the year 2007, the CVD death rates were 103 per 100,000 and 84 per 100,000, respectively ($p<0.05$). Lahti, et al.[15] investigated the Helsinki birth cohort (n= 12,939). PWS (n=204) had a higher risk for hospitalization for coronary heart disease (CHD) (hazard ratio (HR)=1.65, 95% CI 1.03-2.57) and for CHD mortality (HR=2.92, 95% CI 1.70-5.0). Mortality was even higher in women (HR=6.91, 95% CI 2.44-19.59 *vs.* HR=2.35, 95% CI 1.25-4.43). Laursen and Nordentoft,[16] in a population-based cohort study in Denmark found that for PWS (n=978) the mortality rate ratio was increased compared to the general population (1.12, 95% CI 1.08-1.15). Kelly, et al,[17] in a retrospective cohort of 1,686 PWS treated with antipsychotic (AP) medication, found elevated standardized mortality ratio (SMR) in PWS (age- and sex-adjusted SMR=4.02, 95% CI 2.88-5.45) compared to the State of Maryland, US, general population, year 2000 rates. Brown, et al,[18] in a prospective study of 370 PWS found both higher CVD mortality (SMR=2.25, 95% CI 1.59-3.1) and DM mortality (SMR=6.14, 95% CI 1.67-1.57). Kilbourne, et al.,[19] in a case-control study of the 1999 Large Health Survey of Veterans, among 22,817 PWS found CVD mortality to be increased (HR=1.37, 95% CI 1.26-1.49). PWS who died from CVD were more likely to die at a younger age (average age, 68.6 years) than those without a psychiatric diagnosis (76.5 years, $p<0.001$). Tokuda, et al.[20] compared 1,108 PWS to patients without schizophrenia (n=189,049) both admitted to a general hospital in Japan. For PWS SMR was 1.3 (95% CI 0.98-1.7) and odds ratio (OR) for CVD mortality was 2.63 (95% CI 1.2-5.77). Fors, et al.[21] in a case-control cohort study in Sweden compared all PWS living in the northern catchment area in Uppsala in 1991 to persons without schizophrenia (n=1,275) matched on age, sex and living area from the Swedish national population register. PWS had excess CVD mortality in men (relative risk (RR)=2.4, $p=0.003$) but not in women with schizophrenia. Laursen, et al.,[22] in a registry based study of 5.5 million persons born in Denmark found increased mortality from CVD in PWS (SMR=2.07, 95% CI 1.9-2.3).

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* CVD related mortality in this study included deaths due to atherosclerosis, hypertension, coronary heart disease, cerebrovascular disease and aortic aneurysm

Table 2

CVD Risk factors among PWS

Authors	Publication Year	Study Design (years of follow-up /recruitment)	PWS (n)	Comparison Group (n)	Place	Main Findings (p-value/95%CI)
Vancamfort, et al.[23]	2012	Case-control study	80	Healthy volunteers (40) matched on gender, age and BMI	Belgium	Smoking 14.8 *vs* 3.8 cigs/day (p<0.001); Exercised less (326 *vs*. 563 mins of physical activity, p<0.001); MetS 35%; BMI did not differ significantly.
Lee, et al.[24]	2012	Case-control study	100	Community controls (300)	Singapore	MetS OR=2.79 (1.5-5.2)
Morden, et al.[14]	2012	Case-control study (2000-2007)	65,362	Persons without schizophrenia (65,362), matched on age, service access year and location in the VA service	Wales	In first 3 study years: DM 17.9%- 21.1% in PWS, 15.8%-18.5% in comparison group; Obesity 25.6%-29.2% in PWS, 24.1%-27.7% in comparison group. In all years: prevalence of diagnosed HTN, CVD and dyslipidemia was consistently lower in PWS than the comparison group. In 2007, the prevalence of diagnosed CVD was 22.4% in PWS and 27.1% in the comparison group. Diagnosed dyslipidemia doubled from 25.2% in PWS and 26.9% in the comparison group in 2000 to 55.9% and 61.7%, respectively in 2007.
Schoepf, et al.[26]	2012	Case-control study (2000-2007)	679	Age and gender matched patients without schizophrenia hospitalized during the same period (88,778)	Germany	DM related mortality RR=2.2 *vs*. 1.1.

Table 2 contd.

Kodesh, et al.[25]	2012	Historical cohort study (2003-2009)	5,732	General HMO population (2,000,000)	Israel	DM OR=1.9.
Yazici, et al.[28]	2011	Cohort study (12/2004-01/2007)	319	Random sample (urban and rural) general population (4,264)	Turkey	MetS 22.9% *vs.* 9.6% (p=0.004).
Jin, et al.[27]	2011	Cross-sectional study	68	Framingham health study	US	Framingham 10-year risk of CHD 1.79 (1.50-2.07).
Cwastiak, et al.[29]	2011	1999 Large Health Survey of Veterans	15,536	485,625	US	Smoking OR=1.69 (1.63-1.75); No regular exercise OR=0.92 (0.89-0.95); Obesity 1.05 (1.01-1.09).
McClave, et al.[30]	2010	Cross-sectional study – the 2007 National Health Interview Survey (NHIS) of general population	150	Persons without any lifetime specified mental illness (21,545)	US	Prevalence 59.1% (95% CI 49.3%-68.2%).
Vinogradova, et al.[31]	2010	Cohort study - QRESEARCH database, (2000-2005)	257	Persons with DM (43,992)	UK	Age of DM diagnosis 57.2 *vs.* 61.1; Mean BMI 29.8 *vs.* 29.0; Smoking 33% *vs.* 16% (p<0.01 for all comparisons).
Ferreira, et al.[32]	2010	Case-control study	125	Primary health care center users (1,721)	Portugal	Careless diet OR=4.46 (2.9-6.9); Smoking OR=2.5 (1.7-3.6); Sedentary life style OR=1.8 (1.2-2.6); Dyslipidemia OR=1.9 (1.3-2.8); Low HDL OR=2.1 (1.3-3.4); DM OR=0.7 (0.4-1.4); HTN OR=0.4 (0.2-0.7); Over-weight/obesity OR=1.8 (0.8-4.0); MetS OR=1.6 (0.6-4.4).

Table 2 contd.

Saarni, et al.[33]	2009	Cohort study. – Health 2000 Survey-	96	General population without psychosis (7,825)	Finland	Obesity OR=2.3 (1.5-3.6); Abdominal obesity OR=2.2 (1.3-3.6); Higher fat percentage mean difference 3.8% (2.0-5.7).
Kilbourne, et al.[19]	2009	Case control study – 1999 Large Health Survey of Veterans,	22,817	Patients without psychiatric disorder (16,072)	US	Smoking HR=1.32 (1.26-1.39); Inadequate physical activity HR=1.66 (1.59-1.74).
Callaghan, et al.[34]	2009	Population-based cohort study, hospital discharge records (2002-2006)	9,815	Appendicitis patients (9,815) matched on age, sex, average neighborhood income level and amount of follow-up time available	Canada	Smoking 2.08 (1.23-3.5); DM 3.8 (3.1-4.7); Obesity 2.2 (1.5-3.5); Dyslipidemia 4.1 (2.9-5.7).
Weber, et al.[35]	2009	Cohort study – National Hospital Discharge Survey (1979-2003)	26, 279	Patients without schizophrenia (1,936,876)	US	HTN PMR=1.2 (1.1-12); DM PMR=1.2 (1.2-1.3); Obesity PMR=2.0 (1.9-2.1).
Birkenaes, et al.[36]	2007	The Oslo TOP Study (for PWS) *vs.* Oslo Health Study (2000-2001)	163	General population (15,186)	Norway	Smoking 55% *vs.* 28%; Overweight 67% *vs.* 52%; Obesity 24% *vs.* 14%; HTN 61% *vs.* 43%; Low HDL 41% *vs.* 21% ($p<0.001$ for all comparisons); DM 3.3% *vs.* 2.2%, (NS).
Weiss, et al.[37]	2006	Cross-sectional study	214	Patients with DM (4,236)	US	Current smoking 21% *vs.* 12% ($p<0.001$).

BMI = Body mass index; CI = Confidence interval; CVD = Cardiovascular disease; DM = Diabetes mellitus; HMO = Health maintenance organization; HR = Hazard ratio; HTN = Hypertension; MetS = Metabolic syndrome; NHANES = National Health and Nutrition Examination Survey; PMR = Proportional morbidity ratio; PWS = Persons with schizophrenia; RR = Relative risk; SMR = Standardized mortality ratio; VA = Veterans Affairs.

Ib. Cardiovascular risk factors studies (Table 2)

Vancampfort, et al.,[23] in a study of 80 PWS (both hospitalized and outpatients) in Belgium did not find a significant difference in BMI compared to 40 controls without schizophrenia (BMI=26.3 *vs.* 25.7, respectively, p=0.53) . Other risk factors were significantly increased; PWS smoked more (14.8 *vs.* 3.8 cigarettes/day, p<0.001), exercised less (326 *vs.* 563 minutes of physical activity per week, p<0.001), and 35 percent of PWS met the International Diabetes Federation criteria for metabolic syndrome (MetS). In a prospective case control study of 100 PWS from Singapore, Lee, et al.[24] found 46 percent of PWS had MetS, 2.8 times more often than controls (95% CI 1.50-5.2). In a study cited above, Morden, et al.[14] followed 65,362 PWS from the veterans affairs health system in Wales compared to controls without schizophrenia between 2000 to 2006. In the earlier years, DM and obesity were more prevalent among PWS relative to the comparison group. DM affected 17.9 percent to 21.1 percent of PWS in the first three study years and 15.8 percent to 18.5 percent of the comparison group. In those years, the prevalence of obesity was also greater among PWS (25.6% to 29.2%) relative to the comparison group (24.1% to 27.7%). These differences diminished in later years. In all years, the prevalence rates of diagnosed HTN, CVD and dyslipidemia were consistently lower in the schizophrenia than the comparison group. In 2007, the prevalence rate of diagnosed CVD was 22.4 percent in the PWS and 27.1 percent in the comparison group. Both groups experienced a substantial increase in CVD risk factors diagnoses over the study period. Diagnosed dyslipidemia nearly doubled from 25.2 percent in PWS and 26.9 percent in the comparison group in 2000 to 55.9 percent and 61.7 percent, respectively, in 2007. Kodesh, et al.[25] in a historical cohort study compared 5,732 PWS to health maintenance organization members without psychiatric diagnosis in Israel. PWS were more likely to be diagnosed with DM (OR=1.9, significance not mentioned). Schoef, et al.,[26] in a case control study of 679 PWS in Germany found higher prevalence of DM among PWS and higher prevalence of DM in PWS who died. The effect of DM on mortality was twice higher among PWS (RR=2.2, 95% CI 1.4-3.6 *vs.* RR=1.1, 95% CI 1.1-1.2). Jin, et al.,[27] in a cross-sectional study of middle aged and older PWS in the US found that the Framingham ten-year risk of CHD was increased by 1.79 (95% CI 1.5-2.07) compared to the general population. In a cohort study in Turkey, Yazici, et al.[28] found MetS in significantly higher rates in PWS in the younger age group (20-29 years old) compared to the general population (22.9% *vs.* 9.6%, p=0.004). Cwastiak, et al.[29] in the 1999 Large Health Survey of Veterans cohort study of 501,161 individuals in the US, of whom three perferrcent were diagnosed with schizophrenia, found increased rates

of several risk factors: smoking (OR=1.69, 95% CI 1.63-1.75), no regular physical exercise (OR=0.92, 95% CI 0.89-0.95), and obesity (OR=1.05, 95% CI 1.01-1.09).

McClave, et al.[30] reported the lifetime prevalence of smoking in the cross-sectional study of the 2007 National Health Interview Survey (NHIS) in the US general population. The survey included a household interview survey of the non-institutionalized population with 23,393 respondents: 7.8 percent of the general population reported having at least one lifetime diagnosis of selected mental illnesses (i.e., bipolar disorder, phobias) and of those, 150 were PWS. PWS had the highest prevalence of age-adjusted current smoking (59.1%, 95% CI 49.3%-68.2%).

Vinogradova, et al.,[31] in a longitudinal cohort study of 43,992 persons with DM conducted in the United Kingdom, 257 also diagnosed with schizophrenia, found persons with both diagnoses were younger at diagnosis of DM (61 years old *vs.* 65 years old), had a higher mean BMI (29.8 *vs.* 29.0) and more individuals were smokers (33% *vs.* 16%) ($p<0.01$ for all comparisons). Persons with both diagnoses had an increased risk of death compared with those with DM alone (OR=1.5, 95% CI 1.2-2.0). Ferreira, et al.[32] found in a case control study of 125 PWS in Portugal that compared to controls, PWS had increased rates of "careless" diet (as defined in the paper) (OR=4.46, 95% CI 2.9-6.9), smoking (OR=2.5, 95% CI 1.7-3.6), sedentary life style (OR=1.8, 95% CI 1.2-2.6), dyslipidemia (OR= 1.9, 95% CI 1.3-2.8) and low HDL (OR=2.1, 95% CI 1.3-3.4). Rates of DM, over-weight/obesity and MetS did not differ between groups. Surprisingly, HTN was less prevalent in PWS (OR=0.4, 95% CI 0.2-0.7). PWS had higher rate of untreated risk factors, including HTN (OR=3.79, 95% CI 1.63-8.81), DM (OR=3.79, 95% CI 2.06-7.35), and dyslipidemia (OR=6.38, 95% CI 1.73-23.59). A difference with borderline significance was found in the ten-year absolute risk of CVD between cases and controls aged 40 years and older ($p=0.05$). Saarni, et al.,[33] in a cohort study in the Health 2000 Survey of 8,028 persons in Finland, including 96 PWS, found that schizophrenia was associated with obesity (OR=2.3, 95% CI 1.5-3.6), abdominal obesity (OR=2.2, 95% CI 1.3-3.6) and with higher fat percentage (mean difference 3.8%, 95% CI 2.0-5.7) than in the remaining sample. After further adjusting for current AP treatment, education, diet and smoking, schizophrenia remained associated with obesity (OR=1.9, 95% CI 1.1-3.6) and abdominal obesity (OR=3.8, 95% CI 1.5-9.4).

Kilbourne, et al.,[19] in a case-control study of 22,817 PWS in the 1999 Large Health Survey of Veterans in the US, found increased rates of risk factors: smoking (HR=1.32, 95% CI 1.26-1.39) and inadequate physical activity (HR=1.66, 95% CI 1.59-1.74). Callaghan, et al.,[34] in a cohort study

in Canada of 9,815 PWS found that PWS were more likely to be admitted with a diagnosis of CVD compared to persons admitted for appendicitis (HR=1.43, 95% CI 1.22-1.69). PWS smoked more (0.8% *vs.* 0.4%, p<0.001), had higher rates of DM (4.6% *vs.* 1.3%, p<0.001) and dyslipidemia (0.9% *vs.* 0.3%, p<0.001). Weber, et al.,[35] in a cohort study of the National Hospital Discharge Survey, 1979-2003, in the US, found higher proportional morbidity ratio (PMR) of HTN (PMR=1.2, 95% CI 1.1-1.2), DM (PMR=1.2, 95% CI 1.2-1.3), and obesity (PMR= 2.0, 95% CI 1.9-2.1). Birkenaes, et al.,[36] in a study of 163 PWS (from the Oslo Thematic Organized Psychosis (TOP) study) compared to 15,186 persons from the Oslo Health Study 2000-2001, found that PWS smoked more (55% *vs.* 28%), were overweight (67% *vs.* 52%) or obese (24% *vs.* 14%), had HTN (61% *vs.* 43%) and had low HDL (41% *vs.* 21%) (p<0.01 for all comparisons). However, no significant difference was found in DM rates (3.3% *vs.* 2.2%). Weiss, et al.,[37] in a study of 4,236 persons with DM, 214 of them with a diagnosis of schizophrenia, found that PWS were more likely to be current smokers (21% *vs.* 12%, p<0.001).

II. POSSIBLE REASONS FOR EXCESS MORTALITY AMONG PWS

To explain these mortality and risk factors gaps, we reviewed several social and behavioral risk factors that are related to both schizophrenia and CVD.

Effects of anti-psychotic medication on mortality

The effect of AP medication on CVD and mortality (both all-cause and CVD cause) is not clear. AP medication may cause weight gain, dyslipidemia, DM and arrhythmia, however there are contradicting data regarding mortality. We present studies that were found in our literature review and were found relevant to this section.

Otano, et al.,[38] in a prospective observational study of PWS (n=19) in Spain found 26 percent of PWS developed MetS after six months of treatment with AP medication. The postmarketing open label study comparing ziprazidone with olanzepine (ZODIAC)[39] mortality rates after one year of treatment did not find a significant difference in mortality RR. RR ranged according to the definition of CVD mortality (narrow *vs.* broad definition) from 0.38 (95% CI 0.1-1.41) to 1.6 (95% CI 0.84-3.05), respectively. Truyers, et al.[40] in a retrospective cohort study of first episode of psychosis found an increased risk for DM (HR=1.77, 95% CI 1.1-2.83). The risk was significant only for second generation antipsychotic (SGA) medication treated PWS (HR=2.46, 95 %CI 1.29-4.71). Kelly, et al.,[17] in a

retrospective cohort found elevated SMR in PWS treated with antipsychotics (clozapine: OR=4.70, 95% CI 3.19-6.67; risperidone: OR=2.88, 95% CI 1.38-5.30; no significant difference between medications) compared to year 2000 rates for the State of Maryland, US, general population. Woo, et al.,[41] in a retrospective study of PWS treated eight weeks with either clozapine or olanzepine found an increase in both systolic (+3.2 mmHg ±11.3 *vs.* -0.7 mmHg ±8.8, p=0.02) and diastolic (4.2 mmHg ±8.5 *vs.* 0.2 mmHg ±7.9, p=0.002) blood pressure in the clozapine prescribed group. Weight increased in both groups but no change was noted in fasting glucose, cholesterol or triglyceride levels. Jerrel, et al.[42] investigated medical and pharmacy claims of 2,231 PWS in the South Carolina Medicaid program. Rates of obesity, dyslipidemia and DM were lower than the general population, possibly due to under-diagnosis of these conditions. HTN rate was higher among PWS (42% *vs.* 34%, no significance mentioned). The odds of developing these cardio-metabolic sequels did not change after initiation of AP treatment and were not related to any specific AP medication compared to haloperidol.

Tiihonen, et al.,[43] in an 11-year follow-up of mortality in PWS found a decrease in the life expectancy gap between PWS and the general population (22.5 *vs.* 25 years) despite the rise in use of SGA from 13 percent to 64 percent during the follow-up period. All causes mortality was decreased for clozapine compared to perphenazine (HR=0.74, 95% CI 0.60-0.91) and increased for other AP medications (HR=1.45, 95% CI 1.24-1.69). The effect of clozapine was more prominent in mortality rates from suicide (HR=0.34, 95% CI 0.20-0.57). However, CVD mortality rates did not show a significant difference between medications. Newcomer, et al.,[44] in a multicenter randomized double-blind study comparing olanzepine and aripiprazole found after 16 weeks of treatment a decrease in weight (-1.8 *vs.* 1.4, p<0.001), total cholesterol (-9.5 *vs.* -3.3, p=0.005), non-HDL cholesterol (-13.2 *vs.* -2.6, p<0.001) and an increase in HDL cholesterol (1.7 *vs.* -5.9, p=0.002) in the aripiprazole compared to the olanzepine group. Tirupati and Chua,[45] in a cross sectional study of both inpatient and community-based rehabilitation service users (n=221), found the prevalence of obesity in PWS was nearly threefold of the rate reported among Australian adults (59% *vs.* 21%), although the source of data regarding non-PWS population was not mentioned. The prevalence of MetS among the PWS treated with AP medication was more than double the rate observed among Australian adults (68% *vs.* 29%, no significance mentioned). The highest prevalence in MetS was found in patients taking more than one SGA (78%), clozapine with another AP medication (77%), combination of first generation AP medication and SGA (72%), though differences were not significant. Hagg, et al.,[46] in a cross-sectional study in Sweden found that the prevalence rate of MetS was

34.6 percent (95% CI 28.8-40.3), clozapine-treated PWS reached the highest prevalence of MetS (48%, 95% CI 34-62). Joukamaa, et al.,[47] in a 17 years follow-up study based on the Mini-Finland Health Survey (1978-1980) (n=7,217), found that the number of AP medications prescribed at the time of the baseline survey was related to subsequent mortality. Of the 99 PWS, 20 were not taking AP medication at baseline, 31 one drug, 34 two drugs and 14 three drugs or more. The mortality relative risk for PWS taking no neuroleptic, one, two and three or more neuroleptic drugs were 1.29 (95% CI 0.53-3.11), 2.97 (95% CI 1.64-5.38), 3.21 (95% CI 1.93-5.35) and 6.83 (95% CI 3.40-13.71) respectively compared with persons without schizophrenia. Lamberti, et al.,[48] compared outpatients PWS (n=93) with a matched NHANES group of subjects (n=2,701). A total of 50 (53.8%) PWS treated with clozapine met criteria for the MetS, compared to 369 (20.7%, $p<0.001$) subjects within the NHANES group ($\chi^2=47.84$, df=1, $p<0.001$). In a secondary analysis excluding the subgroup with a BMI less than 25 kg/m^2, the prevalence of MetS among NHANES subjects was 34.1 percent, a rate that remained significantly lower than that of the clozapine group ($\chi^2=20.03$, df=1, $p<0.001$).

Socio-economic status (SES) and social fragmentation

Low SES (measured by income and educational level) is associated to both schizophrenia and CVD. Decades of research in different countries and in diverse ethnic groups indicate the inverse association of individual[49] and community/neighborhood[50,51] SES with schizophrenia, with higher prevalence rates among people in lower SES, both in men and women. The ratio of lifetime prevalence of schizophrenia among low *versus* high SES persons was 2.4.[52] Increased schizophrenia incidence rate was found to be in areas of increased inequality.[53] Also, data from high-income countries showed that lower SES, both individual and neighborhood, constitute an elevated risk for CVD morbidity, mortality and poorer prognosis.[54,55] For example, in a European study low SES among adults was found to be independently associated with increased risk of ischemic heart disease mortality in both men and women (RR=1.6, 95% CI 1.5-1.60, and RR=2.1, 95% CI 1.98-2.3, respectively).[56] Beyond individual SES, neighborhood SES, which is the socioeconomic characteristics of the neighborhood in which a person lives, is strongly associated with long-term survival after MI.[57] Data regarding low-income and middle-income countries are less consistent.

In high-income countries, lower SES is also associated with specific CVD risk factors, including: DM,[58-60] even in a relatively highly educated cohort study[61]; HTN[62,63]; obesity[64,65]; and sedentary life style.[64,66] The combined impact of specific CVD individual risk factors on total risk is

multiplicative rather than additive,[67] so there is a markedly increased risk of CVD and rates of premature disease among individuals of low SES.

The impact of SES on CVD risk factors is complex and is probably mediated by interaction of behavioral and modifiable risk factors. Analogous to the classical debate regarding the social causation *versus* the social selection of schizophrenia, there is an on-going debate whether CVD mortality is related to the multiple modifiable behavioral risk factors related to low SES only,[68] or that SES contributes additional risk beyond those risk factors. However, the result is the same. PWS are more likely to be of lower SES and to have increased risk for CVD risk factors and CVD mortality.

Another social indicator that may be involved in the association of CVD and schizophrenia is social fragmentation (measured by the social fragmentation index, SFI). SFI is related to higher incidence of psychosis and schizophrenia.[69-71] This finding was unrelated to neither area-level deprivation nor ethnic composition. Social fragmentation is also associated with CVD risk factors. Data indicate increased incidence of MI in both materially-deprived and socially-fragmented contexts, even when controlled for individual social risk factors.[72] In the Stockholm Heart Epidemiology Program (SHEEP) study, the adjusted RR of MI in the top quartile of materially-deprived areas was 2.0 (95% CI 1.3-3.1) and 1.6 (95% CI 1.2-2.1) for women and men, respectively. Adjusted RR of MI for the top quartile of socially fragmented areas was 1.6 (95% CI 1.0-2.5) for women, and 1.4 (95% CI 1.0-1.8) for men.

Access to and quality of medical care

PWS may suffer from under-diagnosis and under-treatment of their medical co-morbidity.[73] They may be exposed to inferior quality of care in medical health service delivery.[74] PWS may also report lower level of satisfaction from their medical care service.[75] Specifically, there may be a lower level of quality of treatment following MI in PWS. As was shown in a meta-analysis from 2010 following cardiovascular events,[76] PWS have 47 percent lower rates (RR= 0.53, 95% CI 0.4-0.64) of the usual invasive coronary revascularization interventions, with significantly lower receipt of coronary artery bypass graft (CABG) (RR= 0.69, 95% CI 0.55-0.85) and percutaneous transluminal coronary angioplasty (PTCA)/percutaneous coronary intervention (PCI) (RR = 0.50, 95% CI 0.34–0.75). Findings from a recent study that was published after this meta-analysis show similar results; Wu, et al.,[12] as was cited above, in a case-control study of 591 PWS after MI in Taiwan found that when compared to persons without schizophrenia, PWS were less likely to go through catheterization and revascularization after a cardiovascular

event (Adjusted OR=0.37, 95% CI 0.26-0.53 for catheterization, Adjusted OR= 0.35, 95% CI 0.24-0.51 for any PTCA/CABG). This was associated with 2.7 higher inpatient mortality rate for PWS.

There may also be a lower level of quality of medical record management. In a case-control study comparing PWS (n=195) with persons with asthma and the general population, PWS were half as likely as asthma controls and general population controls to have blood pressure (OR=0.51, 95% CI 1.35-0.73) and cholesterol levels (OR=0.50, 95% CI 0.31-0.82) recorded, and were also less likely to have smoking status noted (OR=0.60, 95% CI 0.41-0.85).[77] PWS from the Helsinki birth cohort received less lipid-lowering (HR=0.47, 95% CI 0.27-0.80) and antihypertensive drug treatments (HR=0.37, 95% CI 0.22-0.61).[15] Over time, PWS may experience a low frequency and decreasing trajectory of primary care, as was shown in a retrospective study from the US Veterans Healthcare Administration system[78] of persons with DM only (n=188,332), PWS only (n=40,109), and PSW and DM (n=13,025). Low-decreasing primary care, compared to consistent use, was associated with shorter survival, and it was more prevalent in PWS (73% schizophrenia-only *vs*. 54% schizophrenia and DM *vs*. 52% DM-only). Increasing use, associated with improved survival, was least common among PWS (4% *vs*. 8% schizophrenia-DM *vs*. 7% DM-only). Weiss, et al.[37] who are cited above, found no significant differences in appropriateness of care assessed as: use of a hypoglycemic medication for patients with a glycosylated hemoglobin (HbA1c) level greater than seven percent, use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) by all patients, use of an antihypertensive medication among patients with HTN, use of a lipid-lowering agent among patients with hyperlipidemia, and use of aspirin by all patients. PWS received an overall profile of pharmacological therapy related to cardiac risk factors that was similar to that for persons with DM without schizophrenia. Persons with hyperlipidemia in the two groups were equally likely to receive some form of lipid lowering therapy, however, PWS were significantly more likely to receive one of the older, non-statin agents (OR=1.85, $p<0.05$). Despite appropriate care, there was a significant difference between the two measures of treatment effectiveness: cholesterol levels below 200 mg/dL (OR=0.61, 95% CI 0.45-0.85) and LDL less than 130 mg/dL (OR=0.63, 95% CI 0.42-0.93) were less prevalent in PWS. Nasrallah, et al.[79] found that, in PWS recruited for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, rates of non-treatment ranged from 30.2 percent for DM, to 62.4 percent for HTN, and 88.0 percent for dyslipidemia. Kreyenbuhl, et al.,[80] in a study of 50 PWS with

DM compared to persons with DM alone, found less than half of the persons with DM, both with and without schizophrenia, met recommended goals for cholesterol levels or blood pressure control. PWS with DM were less likely to be prescribed cholesterol-lowering statin medications, ACE inhibitors, and ARB agents compared to persons with DM alone.

There are several suggested possible explanations to this service gap, that may be patient (or disease)-related and physician-related. PWS may have difficulties in interpreting and communicating their somatic symptoms, may express inadequate help-seeking behavior and may avoid discussing their medical issues with health care providers.[81] These stem from schizophrenia symptoms, including cognitive impairment, social isolation and lack of social skills, suspicion or paranoia and negative symptoms (i.e., inactivity, lack of motivation). PWS may perform more poorly when compared to persons without schizophrenia in different intellectual domains (e.g., IQ, attention, memory, language and executive functions).[82] These deficits may begin years before the psychotic symptoms become evident.[83,84] Some authors claimed that these cognitive deficits constitute the core of schizophrenia.[85] Cognitive impairment may affect social cognition.[86]

Understanding the differences between general medical *versus* psychiatric care (fragmentation of health services) and overcoming administrative obstacles may be difficult for PWS.[81] PWS may have difficulties with understanding medical instructions in emergency room settings.[87] This may affect adherence with medical care.

When PWS do seek care, some factors may also make it less likely that they receive good medical care. Medical staff may stigmatize PWS (and their relatives) and hold negative attitudes towards them,[88,89] that may affect decision-making processes. When treating PWS, physical complaints may not be the focus of attention of health providers or may be neglected and misattributed to the psychiatric diagnoses, known as "diagnostic over-shadowing".[90] Physicians may not offer PWS the same treatment plan as they would offer persons without severe mental disorder because of stigma and "therapeutic nihilism", described by PWS and their relatives as abandonment.[91,92]

CONCLUSIONS AND RECOMMENDATIONS

Our review included a diversity of studies with different methodologies (cohort, case-control, retrospective) conducted in different countries. Although this review is time-limited (between 2006-2012) and included only published papers in English, in general, all of the reviewed studies

regarding CVD mortality found that PWS have increased risk of CVD mortality. Additionally, most, but not all of the studies found increased rates of CVD behavioral risk factors (i.e., smoking, sedentary life style/less physical activity, increased BMI) in PWS. Although the international community has declared and endorsed its obligation to protect the rights of persons with mental illness and to promote health care and services to these populations, still PWS are exposed to discrimination, to shorter life expectancy and to worse morbidity outcomes. PWS who are service users and their families, clinicians and policy makers all have the responsibility to correct this situation.

In order to do so, and in light of the special needs and considerations regarding PWS, we outline the following general recommendations. Firstly, severe mental illness such as schizophrenia should be addressed as a CVD risk factor, or "risk equivalent" for CVD.[91] Awareness of this association should be implemented in routine psychiatric and general medicine practice (including internal medicine, family doctors/general practitioners, and cardiology) as well as at national levels for policy makers. Regular screening for cardiovascular risk factors was already recommended by international associations' guidelines.[93] Primary prevention is an important potential in successful CVD mortality reduction in individuals with severe mental illness, although this may be a challenge for clinicians.[94,95]

Secondly, cardiovascular morbidity and mortality should be referred to as a measurable endpoint for treatment. Medical service deliverers should integrate these data with other "traditional" endpoints regarding the treatment of PWS (i.e., survival time in the community, cumulative time in hospital, medication use). This endpoint should be addressed on the research level as well.[93] As our search results indicate, many studies are not epidemiological and do not include a comparison group (25 studies without a comparison group versus 37 relevant studies with comparison).

These two points lead to the conclusion that better integration of medical and psychiatric care of PWS is advisable.[96] Better communication between different physicians (e.g., primary physicians, endocrinologists, and cardiologists) and mental health professionals who treat PWS should be encouraged.[94] This can be accompanied with technological advances (i.e., unified electronic medical record). Understanding of suggested treatment and adherence to recommendations in PWS may be improved if relatives and friends accompany the patient in medical settings.[87]

These recommendations all align with international declarations and with the basic goal of securing the health and health rights of persons who face severe psychiatric disorders.

Acronyms List:
AP = antipsychotic
BMI = body mass index
CVD = cardiovascular disorders
DM = diabetes mellitus
HR = hazard ratio
HTN = hypertension
MetS = metabolic syndrome
MI = myocardial infarction
NHANES = National Health and Nutrition Examination Survey
OR = odds ratio
PMR = proportional morbidity ratio
PWS = persons with schizophrenia
SES = socio-economic status
SFI = social fragmentation index
SGA = second generation antipsychotic medication
SMR = standardized mortality ratio
RR = relative risk

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Dr. Lurie was awarded best poster presentation on his study "Psychosocial Rehabilitation and Time-to-Rehospitalization in Schizophrenia" (Israeli Psychiatric Association, 2012) and an award for outstanding residency achievements (Israeli Psychiatric Association, 2009).

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