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SURVIVE: let the dead help the living—an autopsy-based cohort study for mapping risk markers of death among those with severe mental illnesses

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Abstract:
Background: Forensic autopsy strategies may improve differential diagnostics both post-mortem and ante-mortem and aid in clinical settings concerning preventive efforts for premature mortality. Excess mortality and reduced life expectancy affect persons with severe mental illnesses (SMI) for multi-faceted reasons that remain controversial. Somatic conditions, medical treatment and lifestyle diseases, which are primarily examined in the living, contribute to premature deaths. The underlying pathophysiological mechanisms are unclear, though, and the benefits of a focused, standardised autopsy remain unproven. We have developed and implemented an optimised molecular–biological autopsy for deceased persons with SMI. Our aim is to map the occurrence of 1) somatic diseases and organ changes; 2) metabolic syndrome; 3) use and abuse of alcohol, pharmaceuticals and psychoactive substances; 4) pharmacokinetic and pharmacodynamic factors in the metabolism of pharmaceuticals; and 5) genetic variations (acquired and/or congenital) in sudden cardiac death. Additionally, we hope to contribute to diagnostic treatments and preventive measures to benefit those living with SMI.
Methods: SURVIVE: let the dead help the living is a prospective, autopsy-based study on 500 deceased persons with SMI subjected to forensic autopsies under the Danish Act on Forensic Inquests and Autopsy. The autopsies followed an extended, standardised autopsy protocol comprised of whole-body computed tomography scanning, magnetic resonance imaging of the heart and brain and an extended forensic autopsy, including a wide panel of analyses (toxicology, microbiology, genetics, histology and biochemical analysis). Additionally, post-mortem data were linked to ante-mortem health data extracted from Danish national health registers.
Discussion: The SURVIVE autopsy procedure, including tissue sampling and bio banking, has been shown to be effective. We expect that the SURVIVE study will provide unique opportunities to unravel the mechanisms and causes of premature death in persons with SMI. We also expect that identifying prognostic biomarkers for comorbidities will contribute to prevention of premature deaths and comorbidities in persons with SMI.

Keywords:
Expanded standardised autopsy procedure, molecular autopsy, extended biobanking, premature death markers, severe mental illness

BACKGROUND

Forensic medical research may play a key note in developing strategies to improve differential diagnostics within the field. These strategies can lead to improved clinical diagnostics and preventive strategies for comorbidities and premature mortality in living patients.

In 2010, the Danish Society of Forensic Medicine and the three Danish sections of forensic pathology, based at the universities of Aarhus, Southern Denmark and Copenhagen reported patterns in the causes of death among deceased individuals with severe mental illnesses (SMI) subjected to forensic autopsies [1]. The report was based on a retrospective study on 516 cases with death certificates indicating diagnoses within sections F20-F29 and F30-39 [2] in the 10th edition of the World Health Organization's *International Classification of Diseases* (ICD-10). The cause of death in many cases was intoxication, while 10% died from cardiovascular causes. In 15% of cases, the cause of death could not be determined after autopsies, a higher rate than in other cases undergoing forensic autopsies in Denmark [1].

Based on this, the project SURVIVE: let the dead help the living—an autopsy-based strategy for mapping risk markers of death among those with severe mental illnesses was launched in May 2013. One aim was to introduce a national, standardised, extended forensic autopsy procedure. The SURVIVE algorithm comprises known risk factors for premature death and comorbidities in persons with SMI, along with anthropometric measures, radiological imaging techniques, biomedical status measures and molecular analysis methods.

The population of people suffering from SMI has higher mortality than the general population [3-6]. Among people suffering from, for example, schizophrenia, mortality is more than double [7], and life expectancy is 25 years lower than in an equivalent group of the general population (standardised mortality rate) [8, 9]. Approximately one-thirds of deaths among persons with SMI are caused by suicides and accidents, while the remaining two-thirds result from natural causes, with cardiovascular causes accounting for nearly half of these cases [10, 11].

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However, the underlying reasons for the reduced life expectancy among people with SMI are not sufficiently established. The known risk factors are varied and include cardiovascular diseases (CVD) and lifestyle-related factors, such as diabetes, metabolic syndrome (MetS), obesity, smoking and alcohol and substance use [12-14]. Persons with MetS have increased all-cause mortality and CVD mortality risk [15]. In addition to the risk of intoxication and the detrimental effects of polypharmacy, several antipsychotic and antidepressant pharmaceuticals have been associated with increased risk of sudden cardiac death (SCD) [16-18].

The overall purpose of SURVIVE is to implement an autopsy strategy that can be used to investigate the known risk factors for premature death in a cohort of deceased persons suffering from SMI. These risk factors are lifestyle-associated factors[12], MetS [19], genetic disposition [20], pharmaceuticals [21] and the (ab)use of alcohol and psychoactive substances [22-24]. The aim is to improve differential diagnostics in forensic medicine, clinical diagnostic tools, disease management and treatment in people with SMI within the healthcare sector. No major prospective or systematic autopsy studies have mapped the comorbidities, importance of known risk factors or causes of death in deceased persons with SMI.

RESEARCH QUESTIONS

The objective of SURVIVE is to develop and employ an optimised, molecular–biological autopsy model for deceased persons with SMI to identify the risk factors and causal pathways for sudden and unexpected death. Four main research questions are proposed:

1) What impacts does CVD have on premature death in the study population?
2) What impacts do adipose tissue changes have on the prevalence and severity of CVD?
3) What impacts do medication and substance use have on premature death?
4) Do genetic and epigenetic mechanisms influence medication- and substance-induced cardiac arrhythmia in the study population?

Areas of interest in SURVIVE include but are not limited to:

- patho-anatomical organ changes
- measurable indicators of MetS
- toxicological analyses
- genetic and epigenetic tests for CVD, mental illnesses and drug metabolism
- development of post-mortem radiological methods with post-mortem computer tomography (PMCT), CT angiography and post-mortem magnetic resonance imaging (PMMRI)
- estimation of the representativeness of the SURVIVE populations for Danish patients with mental illness

METHODS AND DESIGN

Design

The SURVIVE study is a national Danish multicentre, prospective, autopsy-based cohort study based at the Department of Forensic Medicine, Copenhagen University, conducted in collaboration with the Department of Forensic Medicine, Aarhus University, and the Department of Forensic Medicine, University of Southern Denmark.

Study period

The study period was 1 May 2013–31 April 2015, and the study sample included 500 deceased individuals (Copenhagen=313, Aarhus=112, Odense=75).

Study population

Inclusion criteria

The project prospectively included all deceased who had known or suspected SMI undergoing forensic autopsy at one of Denmark's three departments of forensic medicine from the 1st of May 2013 and until 500 decedents were included. Upon inclusion of each individual person in the SURVIVE study, the SURVIVE algorithm and workflow were activated. Generally, during the medico-legal inquest, the police decided whether a forensic autopsy should be performed based on the Danish Health Act and the advice of a participating medical health officer or forensic pathologist.

The attending physician determined the presence of SMI or the suspicion of SMI at the time of the medico-legal examination based on information gathered from police reports, next of kin and statements from general practitioners. In some cases, the information was certain and supported a defined diagnosis; in others, it was vague and only indicated suspicion of mental illness. Suspicion included information on treatment with psychotropic pharmaceuticals, defined as prescribed pharmaceuticals with the following codes from The Anatomical Therapeutic Chemical classification system (ATC): N05A, N05B, N06A, N06B and N06C. Decedents receiving N03A pharmaceuticals were included if the indication was due to bipolar or other affective disorders, or the pharmaceutical was N03AE01 (clonazepam). All cases treated with other types of benzodiazepines were included irrespective of the indication. Uncertain information about generic names, tradenames and compounds did not prevent inclusion based on the decision of the attending physician at the department of forensic medicine. The attending physician could at all times confer with a senior physician prior to inclusion or exclusion. Physicians employed by the forensic medical institutes do not have access to the electronic health care files of the health care system and as such, confirmation of a suspicion of SMI was not possible prior to inclusion.

These broad criteria were chosen to avoid missing decedents suffering from an SMI and to include an internal control group of the false positives - decedents without SMI that underwent the same specialised autopsy.

Exclusion criteria

Exclusion criteria were extensive decomposition of the body and if a PMCT scan could not be performed prior to autopsy. Exclusion also happened were the autopsy algorithm would prevent specialised examination required for police investigation (e.g. homicide).Cases in which consent for the SURVIVE project was not given after the autopsy were excluded from further analysis.

Consent

Under Danish legislation, all research protocols involving biological samples from forensic autopsies require informed consent from the next of kin. A

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detailed plan to contact the next of in was accordingly developed. Written information about the SURVIVE study, including the need for consent and instructions how to contact the research team by email or phone, was mailed by post to the next of kin no less than three months after an autopsy was performed. In the case of no reply, a follow-up phone call was made. All information regarding consent, contact information of next of kin and other comments about the information process was recorded in a separate Microsoft Access 2010™ (Microsoft®, Redmond, Washington, USA) database separate from the data registered for the research purposes on each individual case. Cases in which relatives did not give consent were excluded from SURVIVE. Obtaining consent was completed in May 2017, and the consent rate from next of kin was higher than 90%.

Blinding

All cases were assigned a unique project identification (ID) number (SURVIVE-ID) upon inclusion in the study. The case ID numbers and the corresponding data were recorded in an Access database. De-anonymisation was done using a separate table linking the project IDs to the social security numbers of the deceased. Police reports, autopsy reports and correspondence concerning individual cases were not recorded in the database. Case-specific results obtained in the SURVIVE project were not available to investigation of individual cases.

SURVIVE protocol

Post-mortem radiology

All cases were subjected to whole-body PMCT scanning before autopsy at a department of forensic medicine. Either a Siemens CT scanner Somatom Definition, 64 slice or a Somatom Spirit dual slice was used. Scan protocols adhered to the more recent standards from the Danish Accreditation and Metrology Fund (DANAK) following international standard ISO/IEC 17020:2012. The protocols included both routine scans and scans specifically for individual SURVIVE projects (e.g. cardiac CT, lumbar spine and hips for bone mass density (tables 1–4).

SURVIVE scan protocols for PMCT at the three departments of forensic medicine in Denmark **(tables 1–4)**

Table 1. CT scan protocol, Department of Forensic Medicine, University of Copenhagen

	Head and neck	Thorax and abdomen	Lower extremities	Cardiac calcium score	Lumbar spine and hips
mAs	260	90	90	157	200
kV	120	120	120	120	120
Slice (mm)	1.0	3.0	3.0	3.0	3.0
Pitch	0.4	0.24	0.6	0.75	0.95
Kernel	**H20s H60s**	**B31f**	**B31f**	**B30f**	**B50f**

Scanner Siemens Somatom Sensation 4, May–October 2013

Table 2. CT scan protocol, Department of Forensic Medicine, University of Copenhagen

	Head and neck	Thorax and abdomen	Lower extremities	Cardiac calcium score	Lumbar spine and hips	Whole body
mAs	375	47/40	114	147	275	570
kV	140	120	120	120	120	120
Slice (mm)	1.0	3.0/1.0	1.0	3	3.0/1.0	3.0
Pitch	0.75	0.5/0.45	0.85	0.35	0.35	1.5
Kernel	**H20s**	**B30f/B20f**	**B20s/B40s**	**B35f**	**B20f**	**B30f**

Scanner Siemens Somatom Definition, 64 slice, October 2013–May 2015

Table 3. CT scan protocol, Department of Forensic Medicine, University of Aarhus

	Head and neck	Thorax and abdomen	Lower extremities	Cardiac calcium score	Lumbar spine and hips
mAs	500	300	200	210	200
kV	140	120	120	120	120
Slice (mm)	1.0	1.5	1.0	3.0	3.0
Pitch	0.75	0.5	0.85	0.5	0.95
Kernel	**H20s H60**	**B20f B70f**	**B20s B40s**	**B35f**	**B20f**

Scanner Siemens Somatom Definition, 64 slice, May 2013-May 2015

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Table 4. CT scan protocol, Department of Forensic Medicine, University of Southern Denmark

	Head	Neck	Thorax	Abdomen	Lower extremities	Cardiac calcium score	Lumbar spine and hips
mAs	110	110	60	80	30	60	30
kV	130	130	130	130	130	130	130
Slice (mm)	3.0	3.0	5.0	5.0	5.0	3.0	3.0
Pitch	0.95	0.95	1.8	1.8	1.0	1.0	1.0
Kernel	**H31 H60**	**B50**	**B31 B70**	**B41**	**U90**	**B31**	**U90**

Scanner Siemens Somatom Spirit Dual Slice, May 2013-May 2015. Each CT scanner was equipped with a calibration phantom containing different concentrations of hydroxyapatite. The phantoms were supplied by the firm Image Analysis, Inc. Additionally, the CT scanner in Aarhus was equipped with a calibration phantom specifically designed for the measurement of bone mass density by the firm QCT Pro, Mindways Software.

In selected cases, PMCT angiography and PMMRI of the heart and brain were performed.

Extended autopsy algorithm

The standardised autopsy algorithm followed the most recent accredited standards from DANAK. The SURVIVE algorithm built on it by thoroughly describing the registration of physical parameters and anthropometric measurements and the dissection and sampling of each relevant organ (Table 5), focusing on the dissection and registration of heart parameters (Table 6). Dissection of the heart was performed according to international standards [25].

The material needed for registration, sampling and data collection was supplied in an individually assigned cardboard box with a unique SURVIVE-ID. The cardboard box was suitable for the autopsy room and provided before the autopsy. Specifically assigned medical personnel performed all registrations before and during each autopsy (see tables 7–8).

Sampling

The location and sidedness (left or right) of the sample from each organ and tissue were standardised. In addition to the standard autopsy protocol, the samples included peripheral blood and tissue from skeletal muscles, liver, spleen, heart and brain; bone samples from the second lumbar vertebrae and the iliac crest; and hair samples. All tissue and fluid samples were collected in tubes without any additives (15 mL and 5mL, respectively). The relevant samples were stored at -20°C or -80°C until analysis. Tissue for histopathological analyses was fixed in 4% formalin and then embedded in paraffin. Finally, blood was added to DNA filter paper (FTA™ Classic Card, Fitzco, Minneapolis, USA) and stored at room temperature for later analyses.

Sample analysis

Members of the steering group of the SURVIVE-study, who were all certified clinical and forensic pathologists, based histopathological description on a consensus decision. The forensic toxicological analysis after the autopsy was performed at all three forensic chemistry departments following the current DANAK standards under the international standard ISO/IEC 17025:2005. All the toxicological analyses also adhered to an intersectional, approved standard for medication and drug types, analyses matrices and intoxication levels. The analyses comprised screening and quantification of prescribed pharmaceuticals and illicit psychoactive substances, including active metabolites from several samples (Table 9).

Table 5. Registration of physical and organ-specific parameters

Registrations of physical parameters	Organ-specific registrations
Height	Brain weight
Weight	Thyroid weight
Abdominal circumference	Lung weight (left and right)
Hip circumference	Omentum weight
CRP measurement	Kidney capsule weight
Hair length	Spleen weight
Hair treatment	Liver weight
Hair colour	Liver measurements (h x l x d)[a]
	Kidney weight
	Kidney measurements (h x l x d)[a]
	Heart (see Table 6)

[a]h x l x d: height x length x depth

Additional forensic biochemical, microbiological and molecular biology analyses (tables 9 and 10) were performed, including but not limited to post-mortem measurements of blood total cholesterol levels, triglycerides, glycated haemoglobin (HbA1c) and urine-albumin/creatinine ratio.

Other data sources

The 500 cases were supplemented with register-based data from the Danish national health registers (see Table 11) including, but not limited to: information on dispensed prescription medication, contacts with primary health care providers, admissions to hospitals including emergency wards, ambulatory functions and long term admission, use of involuntary commitment in the psychiatric health care system and registration in substance use treatment facilities,

Study outcomes/SURVIVE—an umbrella for several studies

SURVIVE has yielded extensive data and bio sampling serving as entry points for sub-projects relevant to premature death and comorbidities in the population with SMI. Furthermore, the SURVIVE study provides opportunities for the development and improvement of autopsy techniques. To answer the central research questions of the SURVIVE study, several PhD students

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Table 6. Registration of cardiac parameters

Heart	Ventricle measurements (cm)	Ostia circumference (cm)	Coronary artery ostia	Grade of coronary artery disease	Morphological change
Weight (gram)	Left ventricle (anterior, lateral, posterior)	Aorta	Appearance (round, oval or other)	0	None
Measurements A (along the sulcus coronarius) x B (perpendicular to A, from the sulcus coronarius to the apex) x C (height of heart lying on the posterior side, anterior side facing upwards)	Right ventricle (anterior, lateral and posterior)	Mitral	Localisation related to the commissure (above the commissure line, in the commissure line or beneath the commissure line)	1	Fatty streaks
	Septum (from left to right ventricle)	Tricuspid	Localisation related to valve insertion (in insertion, not in insertion)	2	Plaque
		Pulmonary	Patency (dia> 2 mm)	3	Plaque with bleeding
				4	Arteriosclerosis
				5A	Stenosis none
				5B	Stenosis 1%–25%
				5C	Stenosis 26%–50%
				5D	Stenosis 51%–75%
				5E	Stenosis 76%–99%
				5F	**Occlusion 100%**

Table 7. Collection of existing demographic, epidemiological and disease-related data connected to project inclusion

General characteristics	Psychiatric disease	Medication	Related paraclinical values (e.g. biochemistry or ECG)	Lifestyle
Date of birth	Schizophrenia	Antipsychotics	Kidneys	Smoking habits
Date of death	Depression	Antidepressants	Liver	Alcohol abuse
Gender	Bipolar	Other	Thyroid	Drug abuse
Municipality of residence	Other		Heart	
Next of kin			Cholesterol	
Citizenship			CRP	
Ethnicity			**None**	

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and postdocs have been enrolled and started 17 subprojects by December 2017 (Table 12).

Statistical considerations

For each individual subproject, the project team handles the data, supervised by the project manager. Statens Serum Institut, under the Danish Ministry of Health, supports data retrieval and analyses of the national registries. The methods, statistical analysis, programmes and sample size vary among the subprojects. Those involving tissue and fluid analyses use only relevant samples from cases with consent from next of kin, while other subprojects involving only registry- and PMCT/PMMR-scan data have samples from all 500 cases.

Organisation

The SURVIVE study covers all of Denmark and is embedded in a partnership among the three Danish departments of forensic medicine. Project management is handled by the Department of Forensic Medicine, University of Copenhagen. Several specialised teams have been formed, including data management, pathology, psychiatry, toxicology, genetic, post-mortem radiology, cardiology and registry research groups. See the appendix for the participants and collaborators.

DISCUSSION

Extended autopsies of persons with SMI may help uncover a range of conditions highly important for the survival of these persons. The project autopsy algorithm enables investigations, sampling and analyses impossible to perform in the living. Not all organ changes can be detected with radiological imaging, biopsies or surgical interventions. Direct observation of organs and subsequent tissue microscopy, forensic toxicological analysis and molecular biological testing may contribute detailed information that substantially supplements the methods applied to examination of the living. We expect that by optimising the forensic autopsy of deceased persons with SMI, SURVIVE will increase knowledge of somatic disease, organ change, substance abuse, metabolism of pharmaceuticals and acquired and congenital genetic variations. This knowledge may facilitate the prevention of lower life expectancy and higher mortality among persons with SMI. The symptom complex of lifestyle-related disorders in those with mental illness appears to be an exacerbated version of the general population; therefore, we expect general benefits from the SURVIVE results.

LIMITATIONS AND CONCERNS

The medicolegal system setting and the Danish Act on Forensic Inquests limit the number of included cases with SMI. The police decide whether further investigations warrant forensic autopsy. Consequently, the SURVIVE study does not include the deaths of persons with SMI the police decide not to refer for forensic autopsies. Deaths not subjected to legal inquest, such as hospital deaths and clinical autopsies performed in hospital settings, are not included. The included cases thus are subject to selection bias. The SURVIVE inclusion criteria are very broad to ensure forming a sufficiently large group of controls that do not fulfil the criteria for a verified diagnosis within the ICD-10 F2 or F3 sections.

Table 8. Tissue samples for histopathology

Organ	Specific location
Omentum	None
Brain	Frontal cortex
	Hippocampus
	Internal capsule
	Pons
	Medulla oblongata
	Cerebellum
	Hypophysis
Thyroid gland	Lobe
Lung	Superior lobe
	Inferior lobe
Lymph node	Bifurcation
Aorta	Sinus part
	Abdominal part
Spleen	Including capsule
Pancreas	Caput
Liver	Anterior
	Posterior
	Central
Kidney	Parenchymatous width
Suprarenal gland	
Subcutaneous fat	Abdomen
	Buttock
Muscle	M. vastus lateralis
Bone marrow	Second lumbar corpora
Uterus/prostate	-
Ovary/testes	-
Heart	Atrium
	Ventricular ejection area
	Papillary muscle
	Epicardial fat, three areas
	Ventricle anterior
	Ventricle lateral
	Ventricle posterior
	Septum anterior
	Septum posterior
Coronary arteries	Left coronary artery
	Descending branch
	Circumflex branch
	Right coronary artery

SURVIVE is the first Danish forensic research project requiring consent. The setup of the medico-legal system and autopsies required immediate sampling for the study, and it was not possible to ask relatives for informed consent before the autopsies. When contacted several months after the autopsies, many relatives gave consent but also expressed a degree of re-traumatisation by the contact in a situation of grief. Although the final study group of 500 is high by forensic pathology standards, the study group

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Table 9. Aliquot biobank samples and subsequent supplementary analyses

Aliquot biobank samples	Toxicology	Microbiology	Clinical biochemistry
Blood (peripheral and heart blood)	X	X (heart blood)	X
Spinal fluid	X	X	X
Urine	X	-	X
Vitreous humour	X	-	X
Tonsil tissue	X	X	-
Brain tissue	X	X	-
Heart tissue	X	X	-
Liver tissue	X	X	-
Muscular tissue	X	-	-
Lung tissue	-	X	-
Epicardial fat	-	-	-
Omentum	-	-	-
Abdominal fat	-	-	-
Buttocks fat	-	-	-
Blood spot/filter paper	-	X	-
Hair	X	-	-
Tissue for microscopy (see Table 8)	-	-	-
Bone from crista iliaca	-	-	-
Lumbar vertebrae corpus	-	-	-

is small compared to studies among the living [6, 26, 27]. This poses some constraints for the selection of individual research questions.

ABBREVIATIONS

AAU—University of Aalborg
AU—University of Aarhus
CT—computed tomography
CVD —cardiovascular disease
DANAK—Danish Accreditation and Metrology Fund
KU—University of Copenhagen
MetS—metabolic syndrome
MRI—magnetic resonance imaging
PMMRI—post-mortem magnetic resonance imaging
PMCT—post-mortem computed tomography
RH—Rigshospitalet, hospital in Copenhagen
SCD—sudden cardiac death
SDU—University of Southern Denmark
SMI—severe mental illness
SUD—substance use disorder

DECLARATIONS

Ethics approval and consent to participate

The biobank was approved by the Danish Data Protection Agency for Department of Forensic Medicine, University of Southern Denmark (registration number 2013-54-0399), Department of Forensic Medicine, Aarhus University (registration number 2013-54-0400) and Department of Forensic Medicine, University of Copenhagen (registration number 2011-54-1262). Additionally, the project has approval from the National Committee on Health Research Ethics, Denmark (registration number 1305373). Authorisation of data retrieval from several Danish registers was approved by the Danish Data Protection Agency (registration number SUND-2016-06).

Under Danish legislation, all research protocols involving biological samples from forensic autopsies require informed consent from next of kin. Acquisition of consent was completed in May 2017, and the consent rate from next of kin was higher than 90%.

Table 10. Biochemical analyses

Aliquot biobank sample	Analyses
Blood	Triglyceride
	Total cholesterol
	CRP
	HbA1c
	Glucose
Urine	Creatinine
	Albumin

Consent for publication

Not applicable

Availability of data and material

The data supporting the study findings are available from the Department of Forensic Medicine, University of Copenhagen. Access to the data is restricted under the license for the current study. The data are not publicly available.

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Table 11. Danish national health register data on psychiatric, physical state and health issues

Name of national health register	Types of data retrieved for each individual person
National Patient Register	Somatic care: - Admission and discharge dates - Reason for admittance - Diagnoses - Treatment provided Psychiatric care: - Admission and discharge dates - Reason for admittance - Self-harm - Diagnosis - Treatment provided
Register of Medicinal Product Statistics	Medication: - Prescription - Dosage - Date of retrieval of dispensed medication - Indications for prescription
National Alcohol Treatment Register	Alcohol abuse: - Types of abuse - Severity - Substitution medications - Other types of medication
Register of Drug Abusers Undergoing Treatment	Drug abuse: - Types of abuse - Drugs in use - Substitution medications
Involuntary Commitment Register	Psychiatric care: - Start and end date of involuntary commitment - Type of involuntary commitment used (isolation, electro-shock-therapy, medication, etc) - Reasons for involuntary commitment
Danish Psychiatric Central Register	Psychiatric care: - Admission and discharge dates - Reason for admittance - Self-harm - Diagnoses - Treatment provided
Health Security System	**Primary health care system:** **- Contacts** **- Type of primary health care practitioner**

Table 13. Subprojects under SURVIVE as of December 2017

PhD projects	
1	Pato-anatomic organ changes: lifestyle or medication
2	Metabolism and inflammation in fatty tissue
3	Prognostic markers for cardiovascular disease by calcium score and imaging
4	Polypharmacy and arrhythmogenic death
5	Correlation between osteoporosis and treatment with antipsychotic medications
6	Identifying the mechanisms underlying premature death in persons suffering from schizophrenia or severe depression, a registry-based study
7	Hair analysis for medications, illicit substances and the stress cursor cortisol
8	Analysis of medication and illicit substances in tissues and biological fluids to understand the unexpected deaths of mentally ill individuals
9	Stress-related morphological changes
Postdoc projects	
10	Genetic-associated arrhythmias vs sudden cardiac death
11	Heart morphology and MRI, T2 quantification
12	Epigenetics: drug-induced sudden cardiac death among individuals with schizophrenia
Scholarships	
13	Kidney damage: pharmacologically induced kidney injury in individuals with schizophrenia
14	Virtual organ measurement (CT & MRI): method development
15	Obesity and fatty hearts
16	CT-based volumetric study of hippocampus
17	Steatosis myocardii, fatty infiltration in the myocytes

However, data can be made available from the authors upon reasonable requests and with permission from the Danish Data Protection Agency.

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

JBAN and CBH designed the study and obtained funding. JLT, GLO and LWB contributed to the study implementation. CBH, MRC, AGG, AB and CJ contributed to designing and arranging the logistics and implementing the algorithm. CJ, PL and LWB designed the PMCT scan protocols. LKR collected the registry data and drafted the second version of the manuscript. MRC, AGG and CJ obtained consent from the next of kin. AGG analysed all the PMCT scans for calcium scores. CJ and JBAN wrote the first draft of the manuscript. The other authors critically reviewed the manuscript for intellectual content. All the authors read and approved the final manuscript.

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APPENDIX

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