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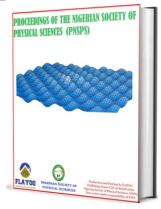

A systematic literature review of multivariate normal variance-mean mixture representations in pharmacokinetic studies

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A B S T R A C T

The NVMM framework is an integrated approach that extends the normal distribution by including heavy-tail properties. In spite rapid methodological advances in this distribution family, large amount of literature only focuses on mixing densities that provide average tail activities which are insufficient in capturing extreme variability that constantly occur in drug pharmacokinetic processes. This study provides an in depth systematic review of literature which focuses on multivariate and few univariate distributions developed using the NVMM approach with particular interest in the baseline distributions such as the normal, Kotz-type, and related distributions. And also, evaluating the different distributions used as mixing variables. This review followed a well-structured PRISMA procedure; the searches for literature related to the study were done with different databases namely PubMed, Web of Science, Google Scholar, Science Direct, and Scopus. From 2,588 retrieved records (between Jan. 1st, 2000 to Dec. 31st, 2025), rigorous screening, eligibility criteria, and quality assessment yielded 17 high-quality studies for synthesis. Data extraction focused on distributional structures, mixing variables, estimation methods, and applications. After using the set criteria for selection, 17 literatures were identified and added to the study database for a qualitative synthesis. Our review showed different forms and alternative distributions that could arise from the normal, skew-normal, Kotz, Laplace, skew-Laplace etc using the NVMM framework. The review showed that distribution tail largely depends on the nature of the mixing variable. Finally, the review showed inadequate extreme variability capturing; suggesting the adaptation of a type II extreme-value distribution.

Keywords: Heavy-tailed distributions, Mixture representations, Multivariate distributions, Systematic review, Variance-mean mixtures.

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1. INTRODUCTION

The multivariate normal variance-mean mixture (NVMM) family of distribution establishes a class of probability distributions use in extending baseline distributions and is capable for capturing heavy tail features present in most multivariate datasets. The multivariate NVMM uses the conditional distribution of any baseline distribution with a stochastic representation of the mean and variance mixed with a non-negative distribution (called the mixing variable). Due to its flexibility, the NVMM incorporate several classical distributions while, still persevering their

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likelihood inference [1–3]. In the development of multivariate probability distribution, this form of probability representation is predominately been used due to its flexibility in tail behavior, complex data structures, and outliers. Different milestone have been achieved relating to theoretical framework in this area which has completely stretched the NVMM framework beyond the first baseline distribution (multivariate normal) [4–7]. For example, multivariate distribution developed using the NVMM include the skew-normal variance-mean mixture, Kotz-type variance-mean mixture, Laplace variance-mean mixture etc. with properties such as moment, characteristic, and moment generating function [8–11]. Similarly, semi-parametric formulations have equally been proposed with the aim of relaxing the parametric assumptions regarding the density used as mixing variable [3, 12]. The extension to semi-parametric method shows that NVMM is a comprehensible framework. Recently, the theoretical aspect on parameter estimation and inference as regards NVMM has been the focus; to this effect different hybrid efficient algorithms for computation have been developed namely randomized quasi-Monte Carlo methods, numerical maximum likelihood, EM- or ECM-type etc. [13, 14]. In resolving some of these computational challenges [15] developed the *nvmix* R package. Thus, the NVMM has been applied to different areas these includes finance/econometric modeling, engineering, biomedical/pharmacokinetic etc. [16–20]. In existing NVMM studies, the dominating mixing variables used include the following gamma, inverse gamma, inverse generalized gamma, generalized inverse Gaussian, Lindley, and Birnbaum-Saunders. Amongst many applied fields such as drug pharmacokinetic (PK) and finance, datasets from these areas are frequently characterized by extreme variability/outliers and skewness features. These data characteristics often challenge the adequacy of mixing variable. Hence, extreme-value distributions or its generalization remain under explored within the NVMM framework.

In this study review, we intend to explore NVMM distributions in the area of pharmacology particularly, in the area of pharmacokinetic as this area deals with drug concentrations and kinetic in the human body; hence, providing room for massive volatility. PK involves the quantification of drugs in the human body based on the following principle; absorption, distribution, metabolism, and excretion and also, the determining drug concentration over time within the same biological host [29]. Furthermore, PK explains the time-course of drug flow after absorption following various compartments which enables the estimation dosing regimens, toxicity, and therapeutic response in clinical processes. Pharmacokinetics (PKs) incorporates mathematical & statistical modelling, experimental data, and physiological principles so as to identify, understand, and quantify variability amongst patients/clinical subjects/clients and the optimization of personalized treatment for outcomes [29, 30]. Generally, PKs offers the scientific and foundational base for coherent drug advancement, therapeutic drug monitoring, and dose formulation in contemporary pharmaceutical study. Thus, since PK datasets originating from drug reactions are volatile thereby exhibiting extreme variability, the NVMM family of distribution is flexible enough to accommodate such data characteristics due to its mixing variable framework.

Currently, literature reviews may possibly be categorized into the following: traditional literature review (TLR), meta-analysis literature review (MLR), and systematic literature review (SLR). The TLR only provides broad summary as well as interpretation of an area/subject without proper or strict methods. MLR involves a quantitative approach that applies statistical/mathematical principles in analyzing data from numerous quantitative studies. While, SLR adopts a pre-defined, credible, and strict/rigorous method to select, assess, and synthesize the precise set research questions. Based on the authors' awareness/findings/knowledge. In summary, this SLR seeks to identify, clarify and abridge the existing evidences concerning (1) the existing variance-mean mixtures, (2) mixing variables used, and (3) their resultant functions and limitations. This SLR review seeks to synthesize studies using the NVMM approach in developing multivariate probability distribution. Therefore, this study will make available and provide insight to researchers in different areas of discipline utilizing probability theories in employing and developing improved distributions.

2. METHODS

This study adopted the method recommended by Ref. [21–23] in implementing this review (see Fig. 1). Accordingly, Fig. 1 showcases the review procedures involve in achieving the research questions; these procedures are in four (4) phases which are as follows: research questions, search design, study selection, and data synthesis. In phase 1, we formulated a couple of research questions in-line with the study aim. In phase 2, we also designed the search design in accordance with the research questions; this phase also involves the search terms and the strategies used in selecting the resources (i.e. literature). While, in phase 3 the review focused on data extraction and resource consideration in-line the quality measures/assessment criteria. And finally, phase 4 focuses on the data synthesis involving final study selection for inclusion and further actions were required.

2.1. RESEARCH QUESTIONS

This SLR is aimed at understanding and summarizing empirical facts regarding NVMM family of distributions, the mixing theory behind the framework, and identifying possible research gaps in resources for research opportunities. In order to accomplish this aim, three (3) research questions (RQs) have been formulated, they are as follows:

1. What are the existing variance-mean mixture representations?
2. What are the existing conditional and mixing distributions?
3. What are resultant functions and their limitations?

These formulated RQs are entwined forming the foundation for this study and were concurrently examined.

2.2. SEARCH DESIGN

The search design as shown in Fig. 1 involved the search terms, resources (i.e. literature), and search procedure. Finally, identified literature were then retrieved and imported into the Rayyan software for additional screening [25].

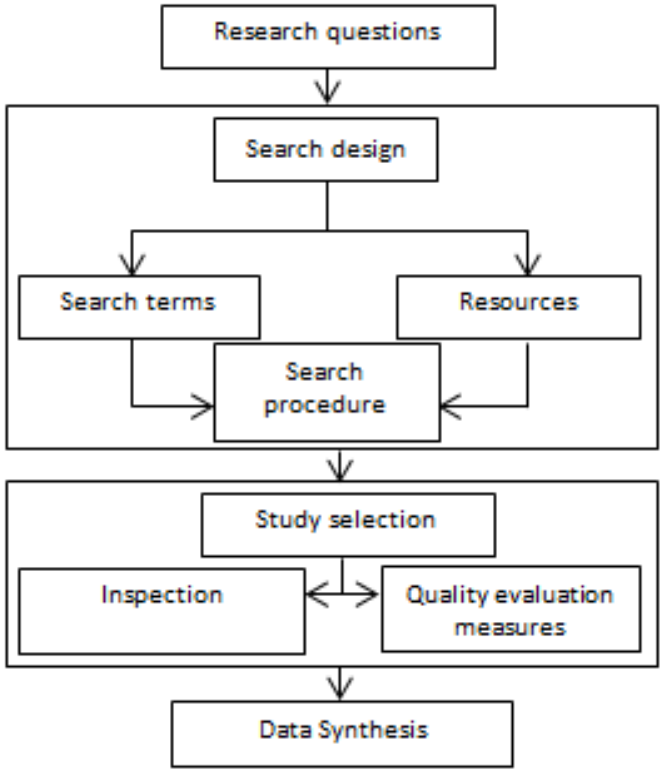

Figure 1. Algorithm for the stages of the review procedure [24].

2.2.1. Search query

The search terms as shown in Table 1 was developed using the following guidelines described in Refs. [21–23] which involves the following:

1. The main terms were derived from the RQs.
2. Synonyms and different spellings for the main terms were identified.
3. Keywords in related and relevant books and papers were equally identified.
4. Boolean operator such as "OR" was used to incorporate synonyms and different spellings.
5. Truncations were done to ensure the search terms were fully utilized to maximized results.

Thus, Table 1 presents the search terms:

2.2.2. Database records

In this study, we employed secondary data which are literature identified and sourced using the search query as shown in Table 1. Accordingly, resources were sourced from the following databases namely PubMed, Web of Science, Google Scholar, Science Direct, Scopus, and other sources. Also, the title and abstract were key components these databases used to conduct the search for peer-reviewed journals, book chapters, proceedings, and workshops/symposiums.

2.2.3. Search procedure

As earlier mentioned, SLR involves a broad search of relevant literature from vital sources concerning the subject matter. Nevertheless, the search procedures adopted in this study includes some steps (see Fig. 2). As listed in Section 2.2.2, five electronic literature databases were used as sources for this search; a full and exhaustive search was conducted on these databases and the retrieved results (i.e. literature) were collected as potential resources. We equally conducted another search in-line with RQs, by going through the reference sections of each prospective study obtained earlier and found additional records that were relevant to records collected initially.

Table 1. Search query.

("normal variance-mean mixture*" OR "variance-mean mixture*" OR mixture distribution* OR variance-mean mixture* OR normal variance-mean*) OR ("Bessel function" OR "Bessel equations" OR Bessel equation* OR Bessel differential*) OR ("heavy-tail*" OR "extreme value distribution*" OR "distributional theor*" OR elliptical distribution*) OR ("pharmacokinetics" OR pharmacokinetic* OR "population PK" OR "population-level PK" OR "pharmacodynamics" OR pharmacodynamics* OR "population PD" OR "population-level PD") OR ("epidemiolog*" OR "disease" OR "public-health" OR "global health" OR "health")

2.3. STUDY SELECTION

As shown in Fig. 2, the results from the PRISM diagram is as follows; PubMed (n = 1,390), Web of Science (n = 161), Google Scholar (n = 317), Science Direct (n = 109), and Scopus (n = 611) amounting to 2,588 records. Before the screening, 2,262 records were removed from the total literature retrieved; out of the 2,262 literature, 2,071 were duplicates, 118 records were marked as ineligible through the automation tools, and 73 records were excluded due to other reasons. While, 326 records were subjected to further screening using the inclusion criteria, quality evaluation measure/assessment questions, and criteria for contents assessment (see Table 2, 3, and 6, respectively). Hence, 25 studies were chosen, while, 9 records were later excluded due to certain reasons as captured in Fig. 2. Finally, 16 records were then selected with an addition of 1 report since it met the eligibility criteria. In all 17 studies were selected and considered capable in providing the relevant answers to the formulated RQs in Section 2.1.

As shown in the PRISMA flow chart presented in Fig. 2, all the selected studies were archived and organized using the Mendeley reference manager for effective screening, tracking, and better citation management.

2.3.1. Inspection

As shown in Fig. 2, 2,588 potential studies were collated. It was considered necessary to further streamline the collated studies into important ones according to the study aim, RQs, and assessment criteria. We first considered the "*title*" and subsequently, the full "*content*" of these studies were concisely studied. Thus, the study excluded all papers that were unable to address one or more of the RQs and also, that couldn't reflect the aim of this study. Furthermore, we only considered resources that were written/or translated and published in English language were chosen

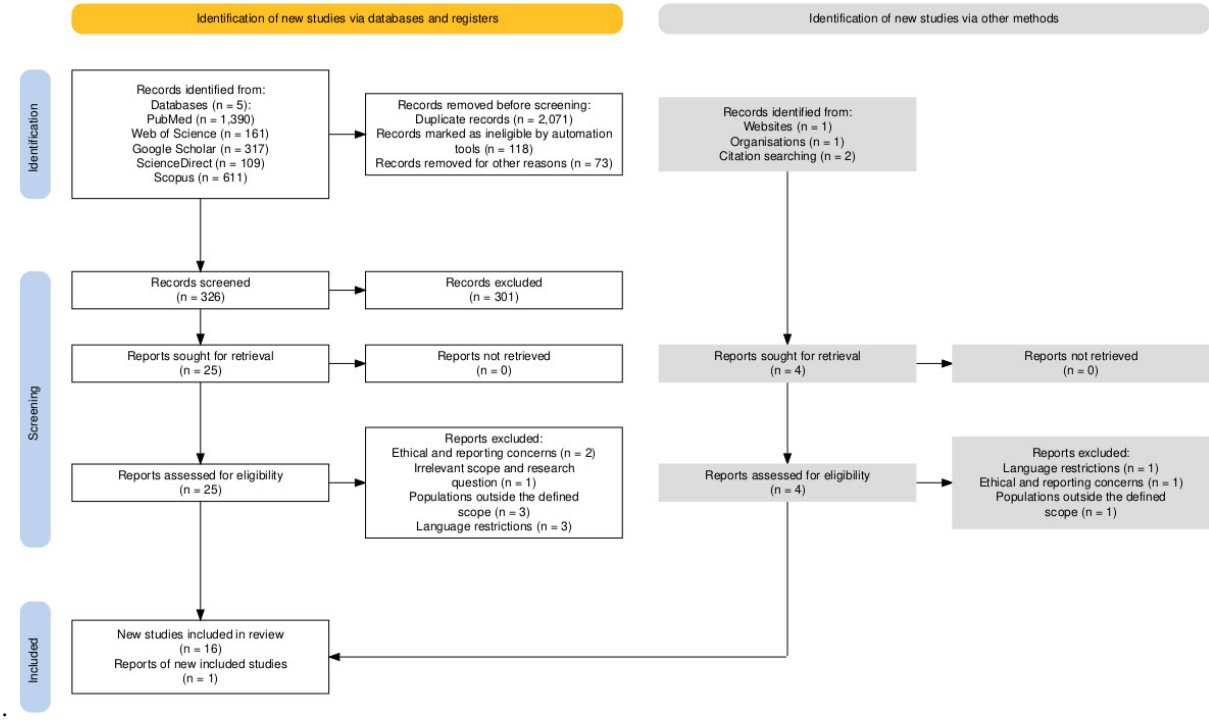

Figure 2. The PRISMA-compliant study selection diagram.

for inclusion into the Rayyan software were we collated the relevant studies. The publish materials are from only journals that are peer-reviewed, books, conference proceedings, symposiums, and workshops. As shown in Fig. 2, duplicate studies appeared the most across the respective databases, but, only the most recent and complete one was included in the study for further scrutiny.

We explicitly performed a SLR for multivariate NVMM representations on studies published between Jan. 1, 2000 to Dec. 31, 2025; thus, the eligibility and screening criteria is given in Table 2.

2.3.2. Quality evaluation measures (quality assessment)

The QAQs of selected literature were attained using a scoring/weighting technique to obtain relevant studies that are capable of providing answers to the stated research questions. A number of QAQs were formulated so as to assess the applicability, relevance, completeness, and credibility of the studies selected.

These QAQs are provided in Table 3; each of the questions formulated has 3 optional responses/answers namely: "yes", "partially" or "no". These options are scored as follows; "yes = 1", "partially = 0.5", and "no = 0". Accordingly, a study total quality score as regards the answers to QAQs is obtained by summing the scores of the respective questions for each selected study. We ensured that the quality evaluation process was accurately implemented, while, discrepancies concerning the quality result of any study was resolved through discussions amongst the authors and consequently reaching unanimous agreement. Hence, the reliability of our findings was attained through the consideration of only relevant studies having the study tolerable quality rate (i.e. the tolerable rate is fixed at been greater than 2, specifying that for a study to be selected, it must have a score higher than 50%). The review excluded 301 studies from the entire collated resources which gave rise to 25 relevant studies; out of this

Table 2. Eligibility and screening criteria.

S/N	Inclusion	Exclusion
i.	Research published between January 1, 2000 and December 31, 2025	Grey literature, comprising works without full bibliographic information (e.g., date, type, volume, or issue) were excluded
ii.	Research articles published in English/or publications available in English	Publications reported in non-English languages
iii.	Studies that focuses on NVMM distributions	Duplicate resources (i.e. only the recent and complete document will be chosen, while, others are excluded)
iv.	All studies that can address one or more of the RQs	Studies that are not related or linked to one or more of the RQs
v.	Studies conducted exclusively on humans across all age ranges	Studies involving animals are excluded
vi.	Studies originating from all countries	Studies based on self-reported data rather than objective measurements or not subjected to peer review

Table 3. Quality assessment questions (QAQs).

S/N	Assessment questions
i.	Are the aims/objectives of the study plainly stated?
ii.	Is the conditional/baseline distribution and mixing variable of the proposed NVMM clearly stated?
iii.	Is the NVMM applied on experimental or simulated datasets?
iv.	Are the properties and behaviour of the proposed/achieved NVMM clearly stated?

Yes = 1 score if the QAQ is answered; Partially = 0.5 score if the QAQ is moderately answered; No = 0 score if the QAQ is not answered.

Table 4. Result summary of the selected studies' quality assessment scores.

S/No.	Record ID	QAQ1	QAQ2	QAQ3	QAQ4	Total Score
1.	P008	1	1	1	0.5	3.5
2.	P011	1	1	1	1	4
3.	P012	1	1	1	1	4
4.	P018	1	1	0.5	0.5	3
5.	P032	1	1	1	0	3
6.	P053	1	0.5	1	0	2.5
7.	P082	1	1	1	0.5	3.5
8.	P083	1	1	1	0.5	3.5
9.	P085	1	1	0.5	1	3.5
10.	P187	1	0.5	1	0	2.5
11.	P210	1	0.5	1	1	3.5
12.	P211	1	1	1	0	3
13.	P213	1	1	1	1	4
14.	P223	1	1	1	1	4
15.	P225	1	1	1	1	4
16.	P229	1	1	1	1	4
17.	P307	1	1	1	1	4

P denote Paper with three digit numbers representing the 326 records initially selected before applying the QAQs; so, after applying the QAQs 17 studies identify under the records ID column were selected as the most relevant articles to the study aim having met the quality assessment target score (e.g. P000).

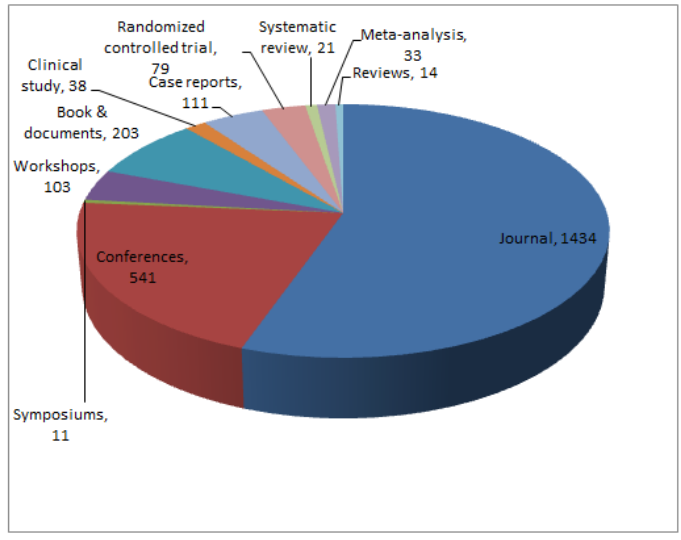

Figure 3. Number of collated resources.

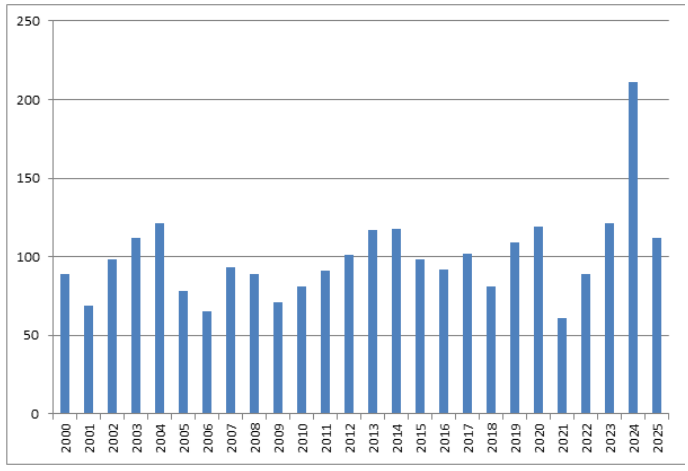

Figure 4. Distribution of publications per year collated from 2000 to 2025.

number, 9 studies were further excluded due to certain reasons as shown in Fig. 2. And finally, 16 records were then selected with an addition of 1 report since it met the eligibility criteria and passed the tolerable rate. These selected studies with their corresponding scores are displayed in Table 4.

While, Table 5 provide an overview of the selected resources; that is, data from each eligible study were organized into a comprehensive summary table (see Table 5). The extracted variables included study title, bibliographic details, study aim/objectives, data sources and type, analytical methods, and findings with possible remarks. Lastly, the QAQs guided the credibility of this review and instrumental in the data synthesis.

2.4. DATA SYNTHESIS

Data synthesis in SLR seeks to evaluate and summarize facts/proofs in connection to the selected studies so as to provide valid response to the RQs. In synthesizing the data, the 17 chosen studies in-line with our formulated QAQs/QAs have been further perused so as to evaluate each study's content in detail (see Table 5). For better result and to improve precision, we have properly synchronized the selected studies' which is the aim of this review.

The data obtained from this study consist of both qualitative and quantitative data. Thus, the complete descriptions concerning the implementation and how the data syntheses were performed are given as follows: data related to RQ1 & RQ2 were structured in a clear approach using various visual tools and various NVMMs were presented in a tabular manner. While, RQ3 involving the resultant functions and their limitations were identified using the selected studies and presented in a tabular manner. The content evaluation measures as presented in Table 6 were useful in conducting data synthesis.

Figure 3 provides the number of literature according to the type of publication, while Figure 4 shows the number of publications from January 1, 2000 to December 31, 2025.

Table 7 and Figure 5 provide the existing NVMMs with their corresponding mixing variable and the visual description of the existing NVMMs according to their respective citation count.

Table 5: My multi-page table caption

S/N	Title	Author's name	Year	Study country	Study objectives	Data sources	Data type	Conditional/ baseline distribution	Distribution of the mixing variable	Key findings/remarks
1.	Bayesian inference and prediction for mean-mixtures of normal distributions	Pankaj Bhagwat and Éric Marchand	2023	No specific country or region	The study seeks to evaluate both the frequentist and Bayesian predictive behaviour for multivariate NVMM and also, derive the Bayesian posteriors	Theoretical construct derived from mathematical analysis	Simulation-based and functional mathematical objects	Multivariate normal distributions	Mean-mixtures	An efficient predictive distributions were developed using the Kullback-Leibler frequentist approach for the skew-normal as well as generalized mean mixture for multivariate normal. A Bayesian with plug-in function shows better predictive accuracy [26].
2.	Multivariate normal variance mixtures in R: The R package nvmix	Erik Hintz, Marius Hofert, and Christiane Lemieux	2022	No specific country or region	The study provide a complete R package named `nvmix`, this new package will be design only for multivariate normal and student t distributions and also, the package will include parameter estimation techniques	15 stock REIT portfolio with data from the SP500 dataset from 2010-01-01 to 2012-12-31 after deGARCHing	Multivariate continuous data. Empirical multivariate datasets	Normal variance-mean mixture distribution	Multivariate normal and t distributions	The study results reveal that the R package developed provides wide relevance especially on practical issues in the areas of quantitative and actuarial science at large. It provides a better modelling of multivariate datasets, and accommodates the identified distribution in the NVMM. Also, the Pareto and inverse-Burr are embedded as mixture the package [15].
3.	Normal variance mixtures: Distribution, density and parameter estimation	Erik Hintz, Marius Hofert, and Christiane Lemieux	2021	No specific country or region	This study seeks to develop an efficient computational technique for the evaluation of joint density and cumulative functions for the NVMM distribution	SP500 index between 2007-01-03 and 2009-12-31 (n = 755 data points in d = 5). The dataset SP500 is obtained from the R package qrmdata	Multivariate continuous data. Empirical multivariate datasets	Multivariate normal variance-mean distribution	Student t distribution	The study showed that for effective and efficient evaluation of the functions, the randomized quasi-Monte Carlo (RQMC) techniques are statistically efficient. Both the multivariate t and normal cases were used for this evaluation. The study showed that convergence is achieved faster using the RQMC for log density computation. Finally, this estimation enables better parameter estimation [13].
4.	Grouped normal variance mixtures	Erik Hintz, Marius Hofert, and Christiane Lemieux	2020	No specific country or region	To identify an efficient computational algorithm for estimating the cumulative and copula functions	Dow Jones 30 index from 1 January 2014 to 31 December 2015 (n = 503 data points obtained from the R package qrm data)	Multivariate continuous data. Empirical multivariate datasets	Multivariate normal variance-mean mixture	Copulas: Grouped and ungrouped t copula	The study reveals that the RQMC methods efficiently estimate the distribution function as well as the copula function. The study also suggest that even at high dimension the RQMC remains efficient [14].
5.	A novel mixture model using the multivariate normal mean-variance mixture of Birnbaum-Saunders distributions and its application to extrasolar planets	Mehrdad Naderi, Wen-Liang Hung, Tsung-I Lin, and Ahad J. Jamalizadeh	2019	No specific country or region	In other to capture asymmetry and fat tail feature in most multivariate datasets, the study proposes a multivariate NVMM with a Birnbaum-Saunders mixing distributions	Extrasolar Planets Encyclopædia (http://exoplanet.eu/)	Both synthetic (simulation-based) and empirical multivariate datasets	Multivariate normal distribution (normal variance-mean mixture)	Birnbaum-Saunders (BS) distribution	In fitting the exo-planet data using the proposed distribution, the study revealed that the new distribution outperforms the multivariate normal distribution. The study showed that the proposed distribution has fat tail properties and can accommodate skewness. The study also showed that a closed form distribution as well as other properties exist [17].

6.	Normal mean-variance Lindley Birnbaum-Saunders distribution	Farzane Hashemi, Mehrdad Naderi, and Ahad Jamalizadeh	2019	No specific country or region	To present a new class of NVMM such that the Lindley Birnbaum-Saunders distribution as the baseline distribution along with a Lindley mixing variable. Hence, the study seeks to extend the Birnbaum-Saunders distribution	Fire insurance claim data set, called beaonre in the R package CASdatasets and Flood stage for two stations on the Fox River in Wisconsin	Both synthetic (simulation-based) and empirical multivariate datasets	Multivariate normal distribution (normal variance-mean mixture)	Lindley Birnbaum-Saunders distribution	The result shows that the new distribution has a closed form expression as well as its moment expressions. The EM-type algorithm provide better goodness-of-fit in modelling lifetime data when compared with existing Birnbaum-Saunders distribution [16].
7.	On the finite mixture modeling via normal mean-variance Birnbaum-Saunders distribution	Mehrdad Naderi, Alireza Arabpou, and Ahad Jamalizadeh	2017	No specific country. The study is purely univariate	To propose a new class of NMVBS-ARCH model as well as its finite mixture of NMVBS (FM-NMVBS)	The study used a flow cytometric data and dataset on flow cytometry in CC4-067-BM.fcs was employed	Both synthetic (simulation-based) and empirical univariate datasets	Univariate normal distribution	Birnbaum-Saunders distribution	Findings from this study showed that the FM-NMVBS can accommodate skewed and heavy tail datasets when matched with the scale mixture skew-normal [18].
8.	Mixture of normal mean-variance of Lindley distributions	Mehrdad Naderi, Alireza Arabpou, and Ahad Jamalizadeh	2016	No specific country. The study is purely theoretical	The aim of the study is to propose a NMVL-MIX finite distribution. Also, some of its properties will be derived and parameters will be estimated via an ECM maximum likelihood methodology. Finally, the proposed distribution will be compared with N-MIX and related mixture such as the skew-normal scale mixture	Flow cytometric data: dataset on flow cytometry in CC4-067-BM.fcs was employed	Both synthetic (simulation-based) and empirical univariate datasets	Univariate normal distribution	Lindley distributions	The NMVL-MIX is proposed based on the NMVL distribution. Results suggest that the new distribution is characterized by heavy tail and skewness. Simulation study indicates that its theoretical properties are appropriate, while, empirical findings show that the distribution is effective for cluster datasets [19].
9.	A framework for normal mean-variance mixture innovations with application to GARCH modelling	P. J. de Jongh and J. H. Venter	2015	No specific country. The study is purely theoretical	The study seeks to introduce new class of error distribution using the NVMM approach. This will be a blend of both the mixing distribution and the normal error distribution	Monthly excess returns series of the US stocks	Simulation-based and empirical datasets	Normal distribution	Normal gamma, normal inverse gamma, normal inverse Gaussian, and normal log-normal	Hence, the study establishes several forms of error distribution using the following mixing variables such as normal gamma, gamma, normal inverse Gaussian, normal log-normal, and normal inverse distributions. The findings reveal that there are predictive and tail similarities amongst the classes of distribution as regards their error components [20].
10.	Variance-mean mixture of the multivariate skew normal distribution	Olcay Arslan	2014	No specific country. The study is purely theoretical	To formulate a new NVMM using multivariate skew-normal distributions with generalized inverse Gaussian	Hourly average wind speed datasets and Australian Institute of Sport (Australian athletes data)	Multivariate continuous data (simulation & empirical multivariate datasets)	Multivariate skew-normal distribution (variance-mean mixture of multivariate skew normal)	Generalized inverse Gaussian distribution	The multivariate skew-normal variance-mean mixture is developed along with its density, moment and characteristic functions. Key findings indicate that the mixture accommodates skewness and heavy tails with superior empirical fit compared to the normal mixture [8].
11.	Normal variance-mean mixtures (i) An inequality between skewness and kurtosis	Werner Hürlimann	2014	No specific country. Purely theoretical	To determine that the squared skewness-to-kurtosis ratio does not exceed the mixing variable's corresponding ratio in NVMM	Theoretical construct derived from mathematical analysis	Symbolic, analytical, and functional mathematical objects	Normal variance-mean mixture	Normal tempered stable, normal inverse Gaussian & variance-gamma	The result indicates that the generalized hyperbolic distribution includes both the log-normal and normal tempered stable mixture. For the NVMM class, the result establishes a generalized skewness-kurtosis inequality [12].

12.	An alternative multivariate skew Laplace distribution: properties and estimation	Olcay Arslan	2010	No specific country. The study is purely theoretical	To revisit the asymmetric Laplace distribution and its generalization and derive some theoretical properties of the distribution	30-years Treasury bonds, Martin Marietta data, and 91 monthly interest rates of an Austrian bank	Both synthetic (simulation-based) and empirical multivariate datasets	multivariate normal distribution (normal variance-mean mixture)	Inverse gamma distribution	Hence, a new alternative multivariate Laplace distribution is developed. Simulation study indicates that the distribution captures skewness better and empirical datasets suggest better likelihood fit compared to the multivariate normal and other forms of Laplace distributions [9].
13.	Variance-mean mixture of Kotz-type distributions	Olcay Arslan	2009a	No specific country. The study is purely theoretical	To develop a new class of NVMM using the Kotz-type distribution as the baseline with generalize inverse Gaussian as the mixture variable	Theoretical construct derived from mathematical analysis	Synthetic (simulation-based) dataset	Multivariate Kotz-type distribution (variance-mean mixture of multivariate Kotz-type)	Generalized inverse Gaussian distribution	A new class of multivariate Kotz-type variance-mean mixture is developed along with derived properties and special cases of the distribution were also identified. Lastly, using both simulated and real dataset, the study reveal slow decay in the tail confirming it as a heavy-tailed distribution [10].
14.	The skew generalized t distribution as the scale mixture of a skew exponential power distribution and its applications in robust estimation	Olcay Arslan & Ali . Genç	2009	No specific country. The study is purely theoretical	To develop an SGT distribution using the scale mixtures as well as examining if it can be obtained also from a generalized gamma variate	Fibre-glass data and Martin-Marietta data	Empirical multivariate datasets	Skew exponential power (SEP) distribution	Skew generalized t (SGT) distribution	The result showed that the developed SGT distribution can accommodate skew and fat-tail datasets. The 2 shape parameters control the peakedness and tail, respectively which highlight their roles in determining the shape and behaviour of the new distribution [27].
15.	A new class of multivariate distribution: scale mixture of Kotz-type distributions	Olcay Arslan	2005	No specific country or region	To develop new class of multivariate NVMM using the Kotz-type distribution as the baseline with inverse generalized gamma as the mixture variable	Theoretical construct derived from mathematical analysis	Symbolic, analytical, and functional mathematical objects	Kotz-type distribution	Inverse generalized gamma distribution	A new class NVMM is developed termed as the Kotz-type variance-mean mixture and several properties were study. The result indicate that the distribution belongs to the elliptical family of distribution which include the multivariate t class [1].
16.	The Laplace distribution and generalizations: a revisit with applications to communications, economics, engineering, and finance	Samuel Kotz, Tomasz J. Kozubowski, and Krzysztof Podgorski	2001	No specific country or region	To reexamine the Laplace distribution and its generalizations in the context of NVMM and their performance across different fields	Theoretical construct derived from mathematical analysis	The type of data considered is both univariate and multivariate continuous data	Multivariate normal distribution (normal variance-mean mixture)	Gamma distribution	The study revealed different forms of Laplace that arises as a result of the NVMM with gamma mixture. The new classes of distribution include asymmetric Laplace and generalized asymmetric Laplace distributions [2].
17.	The semi-parametric normal variance-mean mixture model	Lars Korsholm	2000	No specific country or region	To develop a semi-parametric approach for NVMM by using a semi-parametric mixing distribution	Theoretical construct derived from mathematical analysis	Synthetic (simulation-based) dataset	Multivariate normal distribution (normal variance-mean mixture)	Non-parametric family of distribution	Key findings included the development of an asymptotic normal with an efficient estimator for the Euclidean [3].

ARCH - Autoregressive Conditional Heteroskedasticity; BS - Birnbaum-Saunders; deGARCHing - Standardizing data to remove the GARCH; SLR - Systematic Literature Review
GG - Generalized Gamma; EM - Expectation Maximization; ECM - Expectation Conditional Maximization; TLR - Traditional Literature Review;
FM-NMVBS - Finite Mixture Normal Variance-Mean Mixture Birnbaum-Saunders; GARCH - Generalized Autoregressive Conditional Heteroskedasticity;
MMN - Mean-mixtures of Multivariate Normal; MLR - Meta-Analysis Literature Review; NVM - Normal Variance-Mean;
NVMM - Normal Variance-Mean Mixture; NMVBS - Normal Variance-Mean Mixture Birnbaum-Saunders; NMVL-MIX - Finite Mixture version of the NMV;
NMVL - Normal Mean-Variance Lindley; RQMC - Randomized Quasi-Monte Carlo; SEP - Skew Exponential Power; SGT - Skew Generalized t;

Table 6. Content evaluation measures.

S/N	Selected Study Description
1.	Identification (ID) of bibliographic details of the study, title, year of publication, and source
2.	Study type
3.	Study emphasis
4.	Data aspects
5.	Methodology
6.	Constraints

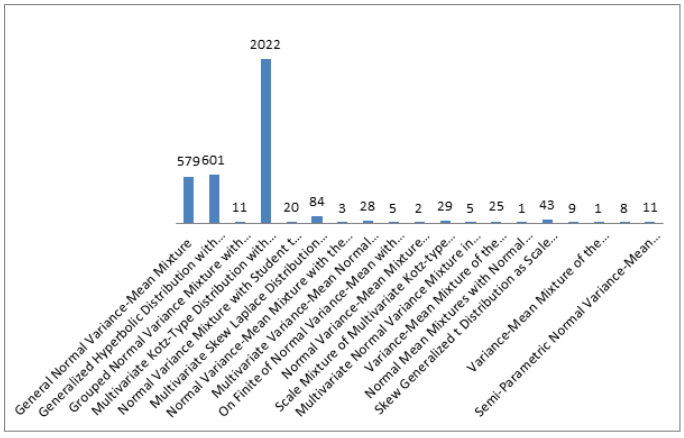

Figure 5. Distribution of citation to existing normal variance-mean mixtures.

2.5. POTENTIAL THREATS TO THE REVIEW'S VALIDITY

This study identified two major threats that could affect the reviewers' validity; these are (i) potential errors in data extraction and (ii) publication bias. We addressed these issues as follows; the reviewers adhere strictly to the search strategy as described in the PRISMA diagram, Table 2, and Section 2.2. Another threat was the tendency of ignoring relevant or related literature because going through the titles, abstracts, or keywords alone might not be enough. In addressing this particular threat, we physically scrutinized the reference section of the shortlisted literature so as to retrieve any relevant literature omitted during the main search.

3. RESULTS AND DISCUSSION

As shown in the PRISMA flow chart, the results are as follows: PubMed (n = 1,390), Web of Science (n = 161), Google Scholar (n = 317), Science Direct (n = 109), and Scopus (n = 611) amounting to 2,588 records. Before the screening, 2,262 records were removed from the total literature retrieved; out of the 2,262 literature, 2,071 were duplicates, 118 records were marked as ineligible through the automation tools, and 73 records were excluded due to other reasons. While 326 records were subjected to further screening, the screening of the 326 records was based on both their title and abstract. Out of 326, 301 records were excluded since they failed to meet the inclusion criteria. Furthermore, the full text for the 25 records was retrieved and successfully assessed; 9 records were later excluded due to certain reasons. Finally, 16 records were then selected with an addition of 1 report since it met the eligibility criteria.

All the selected studies were archived and organized using the Mendeley reference manager for effective screening, tracking, and better citation management.

Table 7. Existing normal variance-mean mixtures with mixing variables and sources.

Baseline/NVMM Distribution	Mixing Variable	Source
General Normal Variance-Mean Mixture	General positive random variable	[6]
Generalized Hyperbolic Distribution	Generalized Inverse Gaussian (GIG)	[4]
Normal Mean Mixtures	Normal Distribution	[26]
Multivariate Normal Variance Mixture in R	Multivariate Normal and Student t	[15]
Grouped Normal Variance Mixture	Copula: Grouped and Ungrouped t Copula	[14]
Multivariate Kotz-Type Distribution	Exponential	[2]
Normal Variance Mixture	Student t	[13]
Multivariate Skew Laplace Distribution	Inverse Gamma	[9]
Normal Variance-Mean Mixture	Normal Tempered Stable, Normal Inverse Gaussian, Hyperbolic Variance-Gamma, and Hyperbolic Skew t	[12]
Multivariate Variance-Mean Normal Distribution	Birnbaum-Saunders	[17]
On Finite of Normal Variance-Mean	Birnbaum-Saunders	[18]
Normal Variance-Mean Mixture Innovation	Normal Gamma, Normal Inverse Gamma, Normal Inverse Gaussian, and Normal Log-Normal	[20]
Variance-Mean Mixture of Kotz-Type Distributions	Extended Generalized Inverse Gaussian	[10]
Mixture of Normal Variance-Mean	Lindley Distribution	[19]
Variance-Mean Mixture of the Multivariate Skew Normal	Generalized Inverse Gaussian	[8]
Skew Generalized t Distribution as Scale Mixture	Skew Exponential Power Distribution	[27]
Scale Mixture of Multivariate Kotz-type Distributions	Inverse Generalized Gamma	[1]
Variance-Mean Mixture of the Multivariate Normal	Weighted Gamma	[28]
Semi-Parametric Normal Variance-Mean Mixture Model	Non-parametric Family of Distribution	[3]

3.1. AN OVERVIEW OF SELECTED STUDIES

The variance-mean mixture approach termed as NVMM improves the robustness of the multivariate normal distribution as regards its tail behaviour [26]. Using simulation, Ref. [26] provided the Bayesian estimation methods for their newly developed skew-normal mean mixtures using an unknown location parameter within the skew-normal distribution.

A new nvmix R package for NVMM was developed by Ref. [15]; the package was meant to improve computational accuracy and reduce the time taken to return results. The authors use both simulated and financial datasets to implement the likelihood inference away from using Gaussian and Student-t distributions; the new package effectively supports numerical density evaluation, distribution functions, and estimation for models using Pareto and inverse-Burr distributions as mixtures. As part of the new methodological advancement in the NVMM framework regarding computational efficiency, Ref. [13] provided a randomized quasi-Monte Carlo algorithms for estimating the parameters of the distribution function, and their study showed improvement in computational speed and accuracy using a high frequency financial dataset. Ref. [17] developed new classes of multivariate NVMM using the Birnbaum-Saunders mixture variable and applied it on an extra-solar planet dataset which is characterized by asymmetric properties. To enhance the robustness of the NVMM distribution, Ref. [16] introduced the Lindley Birnbaum-Saunders distribution. In evaluating the flexibility of the tail, the authors employed both hydrological and insurance datasets. The new distribution achieves a better fit compared to classical mixtures. In handling cluster and skew datasets, Ref. [18] developed new classes of NVMM using the Birnbaum-Saunders distribution called the NMVBS. The new distribution shows robustness to skewness and heavy tails using real-life datasets in cytometry.

A Lindley variance-mean mixture distribution was developed to handle cluster datasets [19], which is a progression from the study of Ref. [18]; the authors used cytometry data as well as simulations in evaluating the tail heaviness of the distribution. The distribution shows significant robustness in handling cluster datasets. As a means of developing new error terms for GARCH models, Ref. [20] developed improved error terms using the normal variance-mean mixture by adopting different mixing variables such as normal-gamma, log-normal, and normal inverse Gaussian; their results indicate that the NVMM is robust enough to propose new classes of error terms. Both simulation and real datasets indicate significant model robustness to volatility in financial markets. The multivariate skew-normal was used to extend the multivariate normal within the variance-mean mixture using a generalized inverse Gaussian mixing, and properties such as moments and characteristic functions were developed [8]. The study showed that the likelihood estimation of the new class outperforms the classical skew-normal distribution. An inequality function that connects both the skewness and kurtosis within the NVMM was developed, showing that the squared skewness to kurtosis ratio is bounded by that of the mixing distribution [12]. An alternative multivariate skew Laplace distribution was developed through extending the NVMM with inverse gamma as a mixture variable [9]; simulation studies and real-life datasets show that the new distribution has more tail robustness.

Hence, in proposing the multivariate Kotz-type variance-mean mixture with a generalized inverse Gaussian mixing variable, Ref. [10] developed a more rigorous distribution that provides more robustness compared to the Kotz-type distribution. While Ref. [1], also using the multivariate Kotz-type variance-mean mixture, used an inverse generalized gamma distribution as a mixing variable to develop new classes of multivariate distributions. In extending the multivariate Kotz-type distribution using the gamma distribution as mixing variables, Ref. [2] obtained a multivariate generalized asymmetric Laplace distribution, which generalizes the multivariate asymmetric Laplace. Lastly, Ref. [3] developed a semi-parametric NVMM using a mixing variable that is from a semi-parametric distribution. The author's semi-parametric NVMM showed significant performance compared to some NVMM distributions as identified in the study. The study also showed that the semi-parametric form of NVMM could be used for complex datasets such as clustered units.

3.2. EXISTING VARIANCE-MEAN MIXTURE REPRESENTATIONS AND MIXING RANDOM VARIABLE (RQ1 & RQ2)

Table 7 and Figure 5 provide an organized synthesis of existing variance-mean mixtures with their corresponding mixing distributions which answers RQ1 and RQ2. These facts reveal that multivariate NVMMs dominate the literature, along with generalized inverse Gaussian, gamma, inverse gamma, generalized inverse gamma, Lindley, and Birnbaum-Saunders serving as basic mixing functions. The review showed that studies such as Refs. [1, 8, 13, 14] revealed that the type of mixing variable used defines and governs the tail heaviness, computational feasibility, and skewness, thus influencing the fundamental properties of the NVMM employed. Theoretical studies comprehensively point out generalized inverse Gaussian, extended generalized inverse Gaussian, generalized inverse gamma, and inverse gamma as well as Birnbaum-Saunders mixtures as the most used mixing variables and multivariate normal and Kotz-type distributions as the most used baseline functions in the variance-mean mixture representation, while estimation is mostly done using EM, RQMC algorithms, and the nvmix package highlighting efficiency and applicability in computation. The result further shows growing research concentration after 2014 (see Figure 4), signifying increasing methodological interest in developing flexible mixing structures. Conversely, the study synthesis further reveals that most NVMMs depend on moderate heavy-tailed mixing distributions, with limited exploration of extreme-value distributions, implying concentration is around classical mixtures, restricting focus on mixing variables with extreme variability.

3.3. RESULTANT FUNCTIONS AND THEIR LIMITATIONS (RQ3)

Collectively, the overview and Table 7 address RQ3 by summarizing the resultant functions obtained from the formulations and their associated limitations within each study's findings. For instance, Arslan (2010, 2014) and Arslan (2009a) developed closed-form densities, characteristic functions, and moments concerning skew Laplace, Kotz-type, and skew-normal NVMMs, while Hintz et al. (2021, 2020) proposed copula functions and efficient density estimation using the RQMC algorithm and nvmix package for R software. In the same way, Naderi

et al. (2019) and Hashemi et al. (2019) derived the ECM/EM based estimation techniques which seek to improve model fitting exhibiting heavy-tailed properties. Despite all these progresses, this review shows that resultant functions ultimately depend on classical mixing variables (see Figure 5 and Table 7), restricting tail extreme features. Several distributions offer little or no robustness to extreme variability situations, particularly in the area of pharmacokinetic (PK) research where drug concentration data exhibit high volatility implying extreme drug absorption or elimination. Accordingly, the review synthesis depicts the need for a robust NVMM framework that incorporates extreme-value mixing variables in achieving more robust resultant functions and enhanced predictive performance in pharmacological modelling across heterogeneous groups.

3.4. RESEARCH GAPS IDENTIFIED

The SLR revealed that existing NVMM studies have considerably improved multivariate distribution theory by integrating various mixing functions (see Table 7). The selected studies reliably exhibit enhanced tail flexibility for skewness, heavy-tailed features, and computational efficiency using the following estimation techniques: RQMC algorithms, EM/ECM, and Bayesian estimation approaches. Though the study outcomes showed that most selected studies highlight moderate heavy-tailed mixing functions and applications in the following areas: biomedical/pharmacology, finance, engineering, general multivariate modeling, etc., with limited emphasis on extreme value phenomena which characterizes PK data. Furthermore, there is a high concentration of NVMM advances around classical mixtures conducted by dominant researchers, progressing methodological continuity rather than innovation in extreme-value mixing. Thus, a major gap emerges due to the dominance of moderate heavy-tail mixtures rather than extreme-value functions, particularly Fréchet-type density, into the NVMM so as to accommodate outliers/high volatility patterns. This review gap indicates and suggests the development of more robust multivariate skewed heavy-tailed NVMM models which are capable of accommodating extreme variability especially in drug concentration as well as treatment response data.

3.5. STUDY LIMITATIONS

3.5.1. Exhaustiveness

While we have conducted a comprehensive review and search strategy employing various databases which includes PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, completeness cannot be assured. The PRISMA chart displays 2,588 retrieved resources which were further reduced to seventeen (17) studies using eligibility criteria and quality assessment, respectively signifying rigorous filtering; hence, highlighting possible exclusion of relevant and related literature on NVMM. Both the search query and data synthesis enhance coverage. Still, only studies published in English are included, our time frame only includes literature within January 1, 2000 to December 31, 2025, and dependence on indexed electronic databases limited search completeness which possibly might exclude unpublished or emerging theoretical contributions in NVMM studies.

3.5.2. Biasness in publication selection

In this review, publication bias is a possible constraint since selected studies are mainly peer-reviewed and exceedingly cited NVMM studies (see Figures 3 and 4). Concentration of these studies in a specific timeframe in the quest of focusing on recent literature may suggest bias. Non-English studies, low assessment scores, and grey literature were excluded.

3.5.3. Data synthesis

Different electronic databases for literature resources in the normal variance-mean mixture framework and related probability distributions were sorted so as to search out and identify studies capable of answering our RQs. We conducted data synthesis using several criteria. Nevertheless, it is important to note that this study cannot guarantee that these measures are fully sufficient in undertaking this section.

4. CONCLUSION

This systematic review focuses on methodological advancement in probability theory, particularly the NVMM family of distributions, highlighting their flexibility and robustness in developing new multivariate distributions emphasising the variance-mean representation. This review has been able to show that NVMM has different forms such as the variance Gaussian mixture, mean mixture, variance mixture, and variance-mean mixture representations; but, even more so, these various forms of stochastic representation have been advanced through rigorous theoretical developments. It can be deduced from this review that NVMM is highly useful in various areas such as finance/insurance, health and biomedical studies, engineering, and ecology. Though this review placed more emphasis on the variance-mean mixture representation compared to the other forms of stochastic representations, our review shows that the variance-mean representation extends the classical normal distribution as well as other classical elliptical distributions into more heavy-tailed families which are capable of capturing asymmetric behaviours. Nevertheless, this study review exposes critical limitations existing within the NVMM formulations; in particular and key is the reliance on mixing distributions that induce only moderate tail behaviour. This constraint is particularly problematic in settings characterized by extreme variability/outliers, a nature of heavy tails that is critical. In providing a solution to the identified gap, this study review establishes a strong and clear motivation for developing a new distribution with the NVMM framework using an extreme-value distribution. Finally, incorporating the Fréchet distribution (one and two parameter) into the multivariate normal and Kotz-type distributions will emerge as a sound theoretical advancement in the NVMM framework offering enhanced densities in modelling pharmacokinetic processes exhibiting extreme variability and skewness.

DATA AVAILABILITY

The data will be available on request from the corresponding author.

References

[1] O. Arslan, "A new class of multivariate distribution: scale mixture of Kotz-type distributions", Statistics & Probability Letters **75** (2005) 18. http://dx.doi.org/10.1016/j.spl.2005.05.009

[2] S. Kotz, T. J. Kozubowski & K. Podgórski, *The Laplace distribution and generalizations: a revisit with applications to communications, economics, engineering, and finance*, Birkhäuser, Boston, 2001. https://doi.org/10.1007/978-1-4612-0173-1

[3] L. Korsholm, ''The semi-parametric normal variance-mean mixture model'', Scandinavian Journal of Statistics **27** (2000) 261. https://doi.org/10.1111/1467-9469.00187

[4] O. Barndorff-Nielsen, ''Hyperbolic distributions and distributions on hyperbolae'', Scand J Stat **5** (1978) 157. http://www.jstor.org/stable/4615705

[5] O. Barndorff-Nielsen, ''Exponentially decreasing distributions for logarithm of particle size'', Proc R Sac Land A **353** (1977) 419. http://www.jstor.org/stable/79167

[6] O. Barndorff-Nielsen, J. Kent & M. Sorensen, ''Normal variance-mean mixtures and z distributions'', Int Stat Rev **50** (1982) 159. https://doi.org/10.2307/1402598

[7] P. Blaesild, ''The two-dimensional hyperbolic distribution and related distributions, with an application to Johannsen' bean data'', Biometrika **68** (1981) 263. https://doi.org/10.2307/2335826

[8] O. Arslan, ''Variance-mean mixture of the multivariate skew normal distribution'', Stat Papers **56** (2015) 378. https://doi.org/10.1007/s00362-014-0585-7

[9] O. Arslan, ''An alternative multivariate skew Laplace distribution: properties and estimation'', Stat Papers **51** (2010) 887. https://doi.org/10.1007/s00362-008-0183-7

[10] O. Arslan, ''Variance-mean mixture of Kotz-type distributions'', Communications in Statistics-Theory and Methods **38** (2009a) 284. http://dx.doi.org/10.1080/03610920802192497

[11] R. P. Browne & P. D. Mcnicholas, ''A mixture of generalized hyperbolic distributions'', The Canadian Journal of Statistics / La Revue Canadienne de Statistique **43** (2015) 198. http://www.jstor.org/stable/44708467

[12] W. Hürlimann, ''Normal variance-mean mixtures (i) an inequality between skewness and kurtosis'', Inequal Appl **2** (2014) 16. http://scik.org/index.php/aia/article/view/1171

[13] E. Hintz, M. Hofert & C. Lemieux, ''Normal variance mixtures: distribution, density and parameter estimation'', Computational Statistics & Data Analysis **157** (2021) 107175. https://doi.org/10.1016/j.csda.2021.107175

[14] E. Hintz, M. Hofert & C. Lemieux, ''Grouped normal variance mixtures'', Risks **8** (2020) 103. https://doi.org/10.3390/risks8040103

[15] E. Hintz, M. Hofert & C. Lemieux, ''Multivariate normal variance mixtures in R: the R package nvmix'', Journal of Statistical Software **102** (2022) 31. https://doi.org/10.18637/jss.v102.i02

[16] F. Hashemi, M. Naderi & A. Jamalizadeh, ''Normal mean-variance Lindley Birnbaum-Saunders distribution'', Statistics and Its Interface **12** (2019) 597. https://dx.doi.org/10.4310/sii.2019.v12.n4.a8

[17] M. Naderi, W. -L. Hung, T. -I. Lin & A. Jamalizadeh, ''A novel mixture model using the multivariate normal mean-variance mixture of Birnbaum-Saunders distributions and its application to extrasolar planets'', Journal of Multivariate Analysis **171** (2019) 138. https://doi.org/10.1016/j.jmva.2018.11.015

[18] M. Naderi, A. Arabpour & A. Jamalizadeh, ''On the finite mixture modeling via normal mean-variance Birnbaum-Saunders distribution'', JIRSS **16** (2017) 51. https://doi.org/10.18869/acadpub.jirss.16.1.1003

[19] M. Naderi, A. Arabpour & A. Jamalizadeh, ''Mixture of normal mean-variance of Lindley distributions'', Communications in Statistics - Simulation and Computation **47** (2018) 1179. http://dx.doi.org/10.1080/03610918.2017.1307400

[20] P. J. De Jongh & J. H. Vent, ''A framework for normal mean variance mixture innovations with application to GARCH modelling'', South African Statist J **49** (2015) 152. https://hdl.handle.net/10520/EJC178084

[21] N. R. Haddaway, M. J. Page, C. C. Pritchard & L. A. McGuinness, ''PRISMA2020: an R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimized digital transparency and open synthesis'', Campbell Systematic Reviews **18** (2022) e1230. https://doi.org/10.1002/cl2.1230

[22] A. Liberati, D. G. Altman, J. Tetzlaff, C. Mulrow, P. C. Gøtzsche, J. P. Loannidis, M. Clarke, P. J. Devereaux, J. Kleijnen & D. Moher, ''The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration'', Annals of Internal Medicine **151** (2009) 94. https://doi.org/10.7326/0003-4819-151-4-200908180-00136

[23] A. H. Lichtenstein, E. A. Yetley & J. Lau, ''Application of systematic review methodology to the field of nutrition. (Prepared by the Tufts Evidence based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 09-0025'', Rockville, MD: Agency for Healthcare Research and Quality **138** (2008) 2297. https://doi.org/10.3945/jn.108.097154

[24] A. N. Azihaiwe-Justin, O. Maduka & C. L. Ani, ''A systematic literature review of approaches on enhancing medication adherence in HIV-positive patients'', Port Harcourt Journal of Public Health **1** (2025) 137. http://phjph.com/index.php/pjph/article/view/38

[25] M. Ouzzani, H. Hammady, Z. Fedorowicz & A. Elmagarmid, ''Rayyan - a web and mobile app for systematic reviews'', Systematic Reviews **5** (2016) 210. https://doi.org/10.1186/s13643-016-0384-4

[26] P. Bhagwat & E. Marchand, ''Bayesian inference and prediction for mean-mixtures of normal distributions'', Electronic Journal of Statistics **17** (2023) 1922. https://doi.org/10.1214/23-ejs2142

[27] O. Arslan & A. I. Genç, ''The skew generalized t distribution as the scale mixture of a skew exponential power distribution and its applications in robust estimation'', Statistics: A Journal of Theoretical and Applied Statistics **43** (2009) 498. http://dx.doi.org/10.1080/02331880802401241

[28] F. Z. Dogru & O. Arslan, ''Variance-mean mixture of the multivariate normal distribution and weighted gamma distribution: properties and applications'', Journal of the Korean Statistical Society **52** (2023) 222. https://doi.org/10.1007/s42952-022-00196-y

[29] L. Shargel, S. Wu-Pong & A. B. Yu, *Applied biopharmaceutics & pharmacokinetics*, 6th ed., McGraw-Hill, 2012.

[30] M. Rowland & T. N. Tozer, *Clinical pharmacokinetics and pharmacodynamics: concepts and applications*, 4th ed., Lippincott Williams & Wilkins, 2011.