Hellenic Complex Systems Laboratory

An Analytical Software for Assessing Uncertainty in Bayesian Parametric Diagnosis in Medicine

Technical Report XXVI

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1. Abstract

The role of medical diagnosis is essential in shaping therapeutic and management strategies in healthcare. Established diagnostic practices typically rely on predetermined clinical criteria and numerical thresholds. In contrast, Bayesian inference provides an advanced framework that supports diagnosis via detailed probabilistic analysis. This study's aim is to introduce a computational tool dedicated to the quantification of uncertainty in the Bayesian posterior probability associated with disease detection, a field that has seen minimal exploration to date. The presented tool is a freely available, specialized computational software that utilizes uncertainty propagation techniques to derive the sampling, measurement, and combined uncertainty in the posterior probability estimates for disease. This innovative software includes two primary modules and fifteen submodules, all designed to facilitate the calculation and graphical representation of the standard uncertainty in the posterior probability estimates for various diseased and non-diseased population samples, incorporating parameters such as the mean and standard deviation of the test measurand, the size of the samples, as well as the components of standard measurement uncertainty inherent in screening and diagnostic tests. Our analysis showcases the software's practical application through the examination of fasting plasma glucose data sourced from the National Health and Nutrition Examination Survey. We validate our findings against the oral glucose tolerance test, a recognized standard in the field. Additionally, our study explores parametric distribution models to assess the uncertainty involved in Bayesian diagnosis, specifically focusing on diabetes mellitus.

Keywords

Bayesian diagnosis; Bayesian inference; prior probability; posterior probability; likelihood; parametric distribution; probability density function; uncertainty; combined uncertainty; measurement uncertainty; sampling uncertainty; combined uncertainty; confidence intervals; diabetes mellitus

2. Introduction

2.1.The Essence of Diagnosis in Medicine

Diagnosis in medicine is fundamentally about identifying the unique characteristics of a disease. The term 'diagnosis,' originating from the Greek 'διάγνωσις' meaning 'discernment' [1], highlights the critical role of distinguishing between healthy and diseased states in individuals. Diagnostic tests are crucial in classifying individuals based on their health status. However, the reliance on a singular threshold for diagnosis across a spectrum of data points introduces uncertainty, owing to the overlapping probability distributions of a measurand in both healthy and diseased groups [2]. While traditional diagnostic methods have been broadly effective, they may not fully encompass the diversity of disease manifestations, particularly in varied populations [3]. As we have highlighted recently [2], Bayesian inference emerges as an attractive alternative, integrating prior disease probabilities with the distribution of diagnostic measurands to calculate posterior probabilities for disease [4–7]. This approach enables a more comprehensive probabilistic assessment [3], the evaluation of the information conveyed by diagnostic measurements, and a personalized patient approach [3,8].

2.1.1. Bayes rule in Medical Diagnostics

Bayesian inference in medical diagnostics is based in Bayes' Rule, a fundamental principle in probability theory [5]. This rule forms a connection between the direct probability of a hypothesis H given specific data E(P(H|E)) and the inverse probability of data E given the hypothesis H(P(E|H)) (Joyce 2021). In medical diagnostics, Bayes' Rule is instrumental in transforming the prior probability of a disease into a posterior probability following diagnostic tests [4].

2.1.2. Challenges in Applying Bayesian Inference

The application of Bayesian inference in diagnostics, however, faces significant challenges:

Uncertainty of Bayesian Posterior Probabilities

A major challenge is addressing the uncertainty associated with Bayesian posterior probabilities for disease, which can significantly impact their clinical usefulness. Accurately estimating, evaluating, and mitigating this uncertainty is critical. To address this, we developed *'Bayesian Diagnostic Uncertainty*' which is the program presented in this study, to facilitate the calculation of the uncertainty of Bayesian probabilities for disease.

Statistical Distributions in Diagnostics

Another challenge involves comprehensively understanding the statistical distributions of diagnostic test measurements in both diseased and nondiseased populations [9]. Accurate calculation of posterior probabilities requires probability density functions (PDF) for the measurand in these populations. The normal distribution, often used for its simplicity, may not be suitable for measurands with non-normal characteristics like skewness or multimodality. Critical evaluation and potential adoption of alternative distributions are necessary for more accurate Bayesian diagnostic methods [9–11]. *'Bayesian Diagnosis'*, our previously published software, addresses this challenge. [2].

Both *'Bayesian Diagnostic Uncertainty'* and *'Bayesian Diagnosis'* significantly enhance the applicability of Bayesian methods in medical diagnostics.

2.1.3. Quantifying Uncertainty in Diagnostics

Uncertainty in diagnostics can be quantified and is often expressed probabilistically [12].

Combined uncertainty

In the context of Bayesian posterior probability for disease, we consider two main components of combined uncertainty:

Measurement uncertainty

This reflects the inherent variability in measurement processes and is defined as a parameter characterizing the dispersion of values that could reasonably be attributed to the measurand [13]. While crucial for laboratory quality assurance, the impact of measurement uncertainty on clinical decision-making and outcomes is often underexplored [14,15], whereas its effect on clinical decision making and consequently on clinical outcomes is rarely quantified [15]. Emerging research focuses on its effects on misclassification [16] and on diagnostic accuracy measures [17].

Sampling uncertainty

The variability in sampling contributes to the uncertainty of posterior probability for disease [18], playing a crucial role in evaluating the reliability of diagnostic methods.

1. Methods

1.1.Computational Methods

1.1.1. Bayes' Rule

Bayes' rule calculates the posterior probability $P(D|T)$ of a disease given a test result x and a parameter vector $\boldsymbol{\theta}$, as follows:

$$P(D|T) = \frac{f_D(x|\boldsymbol{\theta})r}{f_D(x|\boldsymbol{\theta})r + f_{\bar{D}}(x|\boldsymbol{\theta})(1-r)}$$

Here r denotes the prior probability for disease , $f_D(x|\boldsymbol{\theta})$ the PDF in disease presence, while $f_{\bar{D}}(x;\ \boldsymbol{\theta})$ denotes the PDF in its absence (refer to Appendix I for details).

1.1.2. Parametric Distributions

Parametric statistics operate under the assumption that data from a population can be accurately represented by a probability distribution with a fixed set of parameters [19]. The program supports the following parametric distributions:

1. Normal Distribution
2. Lognormal Distribution
3. Gamma Distribution

3.1.1. Uncertainty Quantification

Uncertainty in input parameters can manifest as standard uncertainty $u(x)$, the standard deviation of x, and expanded uncertainty $U(x)$, a range around x encompassing x with a probability p [14].

Measurement Uncertainty in Means and Standard Deviations

Standard measurement uncertainty is computed following guidelines in the "Guide to the expression of uncertainty in measurement" (GUM)[13] and "Expression of measurement uncertainty in laboratory medicine" [14]. Bias is considered a component of this uncertainty [20].

The relationship between the standard measurement uncertainty $u(x)$ to the value of the measurand x, is generally expressed as:

$$u_m(x) = \sqrt{b_0^2 + b_1^2 x^2}$$

where b_0 is a constant and $b_1$is a proportionality constant [21].

If needed, it is approximated linearly as:

$$u_m(x) \cong b_0 + b_1 x$$

Sampling uncertainties of means and standard deviations

If m_P *and* s_P are the mean and standard deviation of a measurand in a population sample of size n_P, then the standard sampling standard uncertainties of m_P *and* s_P are approximated as:

$$u_s(m_P) \cong \frac{s_P}{\sqrt{n_P}}$$

$$u_s(s_P) \cong \frac{s_p}{\sqrt{2(n_P - 1)}}$$

Sampling uncertainty of prior probability for disease

If n_D and $n_{\bar{D}}$ are the respective numbers of diseased and nondiseased in a population sample, then the standard uncertainty of the prior probability for disease $r = \frac{n_D}{n_{\bar{D}}+n_D}$ is approximated as:

$$u_s(r) \cong \sqrt{\frac{(2 + n_{\bar{D}})(2 + n_D)}{(4 + n_{\bar{D}} + n_D)^3}}$$

using the Agresti-Coull adjustment of the Waldo interval [22].

Combined uncertainty of posterior probability for disease

The standard combined uncertainty $u_c(x)$ of posterior probability for disease is computed via uncertainty propagation rules, employing a first-order Taylor series approximation [23].

When there are l components of uncertainty, with standard uncertainties $u_i(x)$, then:

$$u_c(x) = \sqrt{\sum_{i=1}^{l} u_i(x)^2}$$

3.1.2. Expanded uncertainty of posterior probability for disease

The effective degrees of freedom v_{eff} of the combined uncertainty $u_c(x)$ are calculated using the Welch–Satterthwaite formula [24,25]:

$$v_{eff}(x) \cong \frac{u_c(x)^4}{\sum_{i=1}^{l} \frac{u_i(x)^4}{v_i}}$$

If v_{min} the minimum of $v_1, v_2, \ldots, v_l$ then:

$$v_{min} \leq v_{eff}(x) \leq \sum_{i=1}^{l} v_i$$

If $F_v(z)$ is the Student's t-distribution cumulative distribution function with v degrees of freedom and $u_c(x)$ is the standard combined uncertainty of posterior probability for disease, its expanded combined uncertainty $U_c(x)$, at a confidence level p, is computed as:

$$U_c(x) = \left(F_v^{-1}\left(\frac{1-p}{2}\right)u_c(x), F_v^{-1}\left(\frac{1+p}{2}\right)u_c(x)\right)$$

The resultant confidence interval of x, at the same confidence level p, is:

$$CI_p(x) = \left(x + F_v^{-1}\left(\frac{1-p}{2}\right)u_c(x), x + F_v^{-1}\left(\frac{1+p}{2}\right)u_c(x)\right)$$

3.2. The Program

3.2.1. Program Overview

To compute the uncertainty of Bayesian posterior probability for disease, the software program *'Bayesian Diagnostic Uncertainty'* was developed in Wolfram Language, using Wolfram Mathematica®

Ver. 13.3.1[1]. *'Bayesian Diagnostic Uncertainty'* was designed to provide two modules with fifteen submodules, for calculating and plotting the standard sampling, measurement, and combined uncertainty and the resultant confidence intervals of the Bayesian posterior probability of a screening or diagnostic test (See Figure 1).

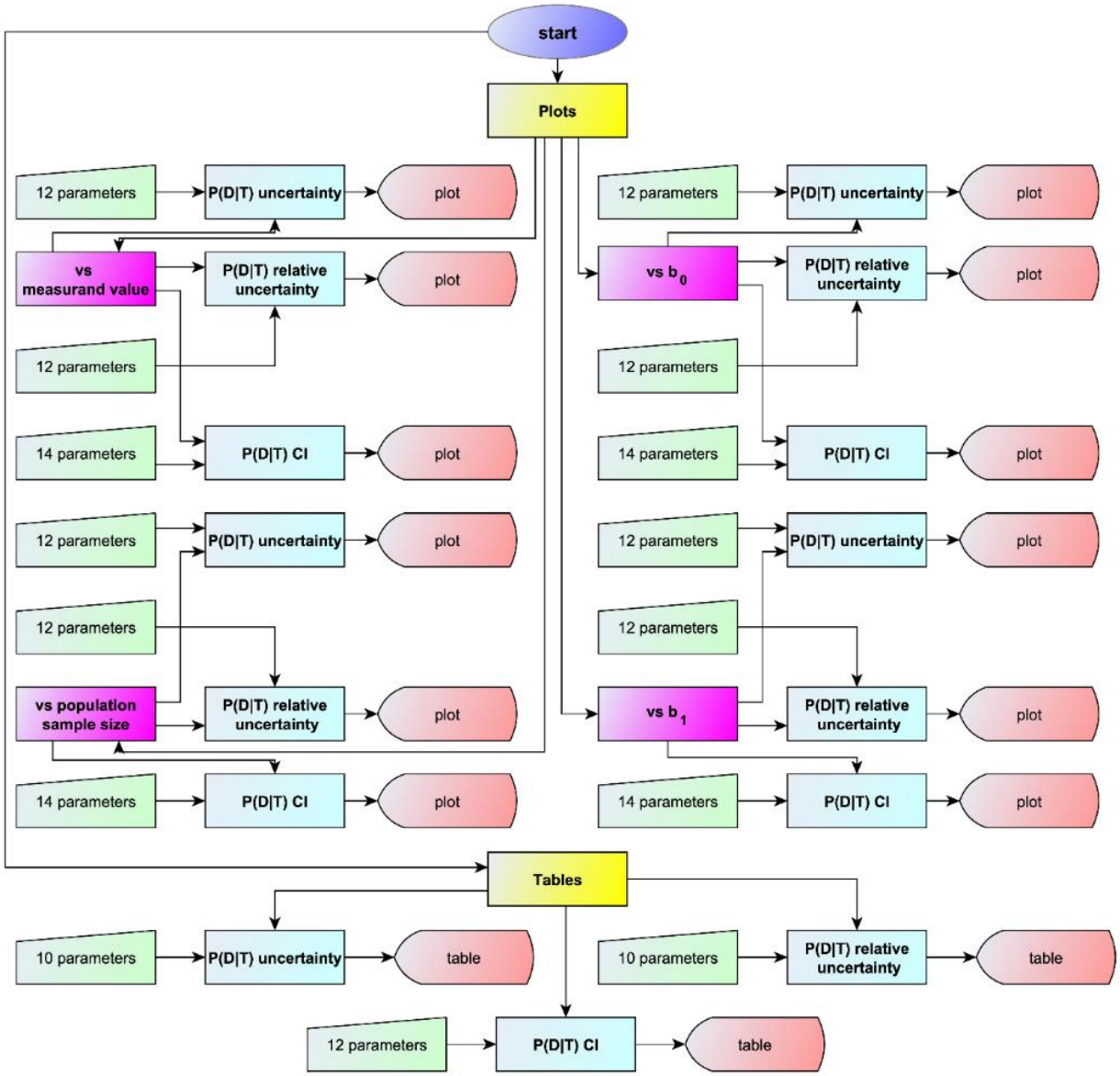

Figure 1. *A simplified flowchart of the program 'Bayesian Diagnostic Uncertainty' with the number of the input parameters and of the output types for each submodule.*

This interactive program is freely available as a Wolfram Language notebook (.nb) (Supplementary file BayesianUncertainty.nb). It can be run on Wolfram Player® or Wolfram Mathematica® (see Appendix II). Due to the complexity of the calculations required, it is computationally intensive.

[1] Wolfram Research, Inc., Mathematica, Version 13.3.1, Champaign, IL (2023).

3.2.2. Input Parameters

To facilitate a diagnostic model, the program allows for the definition of three parametric distributions of a mesurand for the diseased and nondiseased populations.

1. *Distribution Selection*: The user selects the type of distribution of each population from a predefined list:
   1.1. Normal Distribution
   1.2. Lognormal Distribution
   1.3. Gamma Distribution
2. *Definition of Statistical Parameters*: For each population, the user defines its size *n*, and the mean μ and standard deviation σ of the measurand.

Measurement Uncertainty

The user defines the constant contribution b_0 to the standard measurement uncertainty, the proportionality constant b_1 and the number of quality control samples that have been analyzed for its estimation.

3.2.3. Output Specifications

Visualizations

The program generates a series of plots designed to elucidate various uncertainty measures and statistics:

1. *Uncertainty of Posterior Probability for Disease* : Plots are generated to show the standard sampling, measurement, and combined uncertainty of the posterior probability for disease .
2. *Relative Uncertainty of Posterior Probability for Disease* : Plots are generated to show the relative standard sampling, measurement, and combined uncertainty of the posterior probability for disease.
3. *Confidence Intervals of Posterior Probability for Disease* : Plots are generated to show the confidence intervals of the posterior probability for disease .

Tables

1. *Uncertainty of Bayesian Probability for Disease* : The program tabulates the standard sampling, measurement, and combined uncertainty of the posterior probability for disease for a user defined measurand value and for each combination of parametric distributions of the diseased and nondiseased populations.
2. *Relative Uncertainty of Posterior Probability for Disease* : The program tabulates the relative standard sampling, measurement, and combined uncertainty of the posterior probability for disease for a user defined measurand vale and for each combination of parametric distributions of the diseased and nondiseased populations.
3. *Confidence Intervals of Posterior Probability for Disease* : The program tabulates the confidence intervals of the posterior probability for disease, for a user defined confidence level.

By providing this comprehensive set of input parameters and output specifications (see Figure 2), the program offers a robust platform for exploring the uncertainty of Bayesian diagnosis of disease using parametric distributions of medical diagnostic measurands.

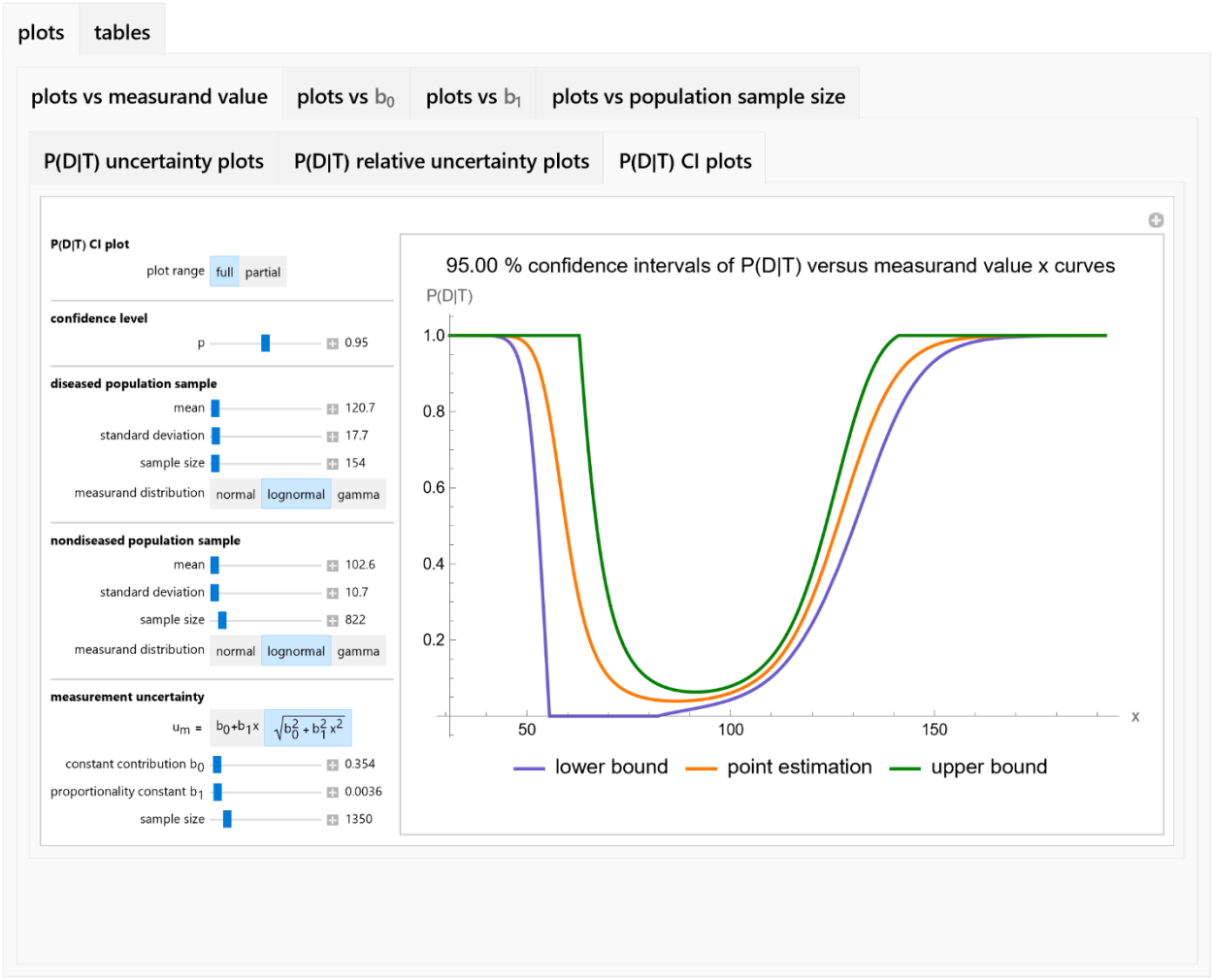

Figure 2: *A screenshot of the program 'Bayesian Diagnostic Uncertainty. The mean measurement uncertainty for the nondiseased (nondiabetic) population equals to 0.5% of the mean measurand (FPG) value observed in this group.*

4. Illustrative Case Study

To demonstrate the application of the program, fasting plasma glucose (FPG) was used as the diagnostic test measurand for the Bayesian diagnosis of diabetes mellitus. The oral glucose tolerance test (OGTT) was used as the reference diagnostic method. A diagnosis of diabetes was confirmed if the plasma glucose value was equal to or greater than 200 mg/dl, measured two hours after oral administration of 75 g of glucose [26], during an OGTT (2-h PG). It is noteworthy that the study population was confined to individuals aged between 70 and 80 years, a decision guided by the well-documented strong correlation between age and the prevalence of diabetes [27].

National Health and Nutrition Examination Survey (NHANES) data from participants was retrieved for the period from 2005 to 2016 [28] (n = 60,936). NHANES is a series of studies designed to evaluate the health and nutritional status of adults and children in the United States.

The inclusion criteria for participants were:

1. Valid fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT) results (n=13,836).

2. A negative response to NHANES question DIQ010 regarding a diabetes diagnosis [29] (n=13,465).
3. Age 70 – 80 years (n = 976).

Participants with a 2-h PG measurement ≥ 200 mg/dl were considered diabetic (n = 154).

The prior probability for diabetes was estimated as

$$v = \frac{154}{976} = 0.158$$

The statistics of the FPG datasets are presented in Table 1. Hereafter, FPG and its uncertainty are expressed in mg/dl.

	Diabetic Patients	Nondiabetic Patients
n	154	822
Mean	120.7	102.6
Median	117.0	102.0
Standard Deviation	19.1	10.9
Skewness	1.448	0.523
Kurtosis	6.354	3.445

Table 1: *The descriptive statistics of the FPG datasets.*

Lognormal distributions were estimated to model FPG measurements in diabetic and nondiabetic participants, using the maximum likelihood estimation method [30]. The respective distributions, parametrized for their means μ_D and $\mu_{\bar{D}}$, and standard deviations σ_D and $\sigma_{\bar{D}}$, were the following:

$$L_D = Lognormal(\mu_D, \sigma_D) = Lognormal(120.671, 17.720)$$

$$L_H = Lognormal(\mu_{\bar{D}}, \sigma_{\bar{D}}) = Lognormal(102.642, 10.653)$$

NHANES quality control data of the FPG measurements was retrieved for the same period (2005-2016). 1350 QC samples had been analyzed. The weighted nonlinear least squares analysis [31] yielded the following function relating the standard measurement uncertainty $u_m(x)$ to the measurement value x:

$$u_m(x) = \sqrt{b_0^2 + b_1^2 x^2} = \sqrt{0.7501 + 0.00012x^2}$$

where $b_0 = 0.866$ and $b_1 = 0.109$.

The means of the standard uncertainty of the FPG of the included diabetic and nondiabetic participants were calculated as follows:

$$\hat{u}_D = 1.586$$

$$\hat{u}_{\bar{D}} = 1.028$$

Consequently, the distributions of the measurands, assuming negligible uncertainty, were approximated as:

$$l_D \cong Lognormal\left(\mu_D, \sqrt{\sigma_D^2 - \hat{u}_D^2}\right) = Lognormal(120.671, 17.720)$$

$$l_{\bar{D}} \cong Lognormal\left(\mu_H, \sqrt{\sigma_{\bar{D}}^2 - \hat{u}_{\bar{D}}^2}\right) = Lognormal(102.642, 10.653)$$

Table 2 displays the descriptive statistics of the estimated lognormal distributions of the diabetic and nondiabetic populations, including the respective p- values of the Cramér-von Mises goodness-of-fit test [32].

	Diabetic Participants		Nondiabetic Participants	
Mean Uncertainty	1.586	0	1.028	0
Mean	120.7	120.7	102.6	102.6
Median	119.4	119.4	102.1	102.1
Standard Deviation	17.8	17.7	10.9	10.7
Skewness	0.446	0.444	0.315	0.312
Kurtosis	3.355	3.352	3.177	3.174
p-value (Cramér-von Mises test)	0.294	0.295	0.281	0.299

Table 2: *The descriptive statistics of the estimated lognormal distributions of the diabetic and nondiabetic participants.*

Figures 3 and 4 show the PDFs of FPG in diabetic and nondiabetic patients and the histograms of the respective NHANES datasets.

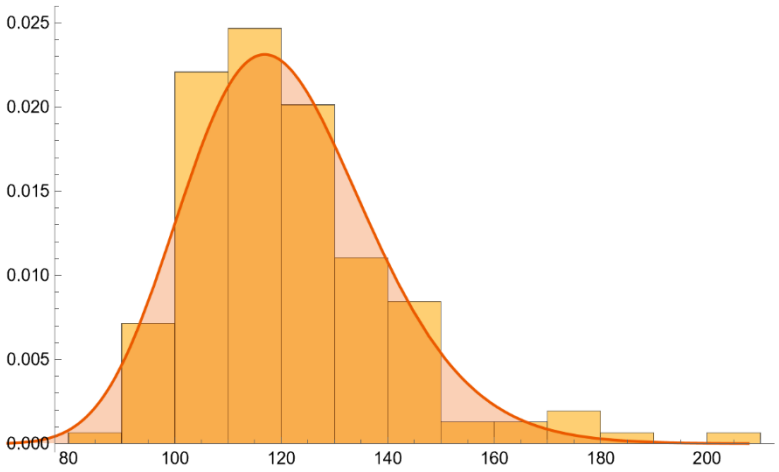

Figure 3. *The PDF of the FPG in diabetic participants, assuming a lognormal distribution and negligible measurement uncertainty, and the histogram of the respective NHANES dataset, with the parameters of the distribution in Table 2.*

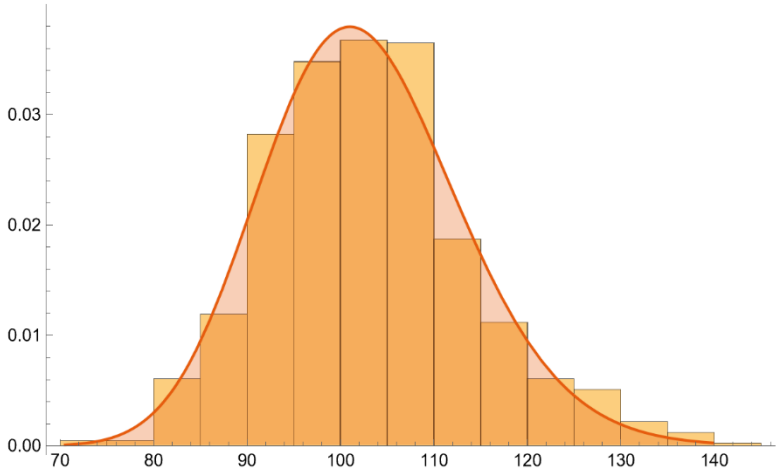

Figure 4. *The PDF of the FPG in nondiabetic participants, assuming a lognormal distribution and negligible measurement uncertainty, and the histogram of the respective NHANES dataset, with the parameters of the distribution in Table 2.*

Likelihoods and posterior probabilities were estimated accordingly.

5. Results

Using the settings of Table 3, the program generated the plots of Figures 5-16 and the tables of Figures 17-19.

Settings	Fig 5-6	Fig 7	Fig 8-9	Fig 10	Fig 11-12	Fig 13	Fig 14-15	Fig 16	Fig 17-18	Fig 19
p	-	0.95	-	0.95	-	0.95	-	0.95	-	0.95
x	31.0– 192.0	31.0– 192.0	126.0	126.0	126.0	126.0	126.0	126.0	126.0	126.0
μ_D	120.7	120.7	120.7	120.7	120.7	120.7	120.7	120.7	120.7	120.7
σ_D	17.7	17.7	17.7	17.7	17.7	17.7	17.7	17.7	17.7	17.7
n_D	154	154	154	154	154	154	-	-	154	154
$\mu_{\overline{D}}$	102.7	102.7	102.7	102.7	102.7	102.7	102.7	102.7	102.7	102.7
$\sigma_{\overline{D}}$	10.7	10.7	10.7	10.7	10.7	10.7	10.7	10.7	10.7	10.7
$n_{\overline{D}}$	822	822	822	822	822	822	-	-	822	822
n	-	-	-	-	-	-	65-5000	65-5000	-	-
r	-	-	-	-	-	-	0.158	0.158	-	-
b_0	0.866	0.866	$0.0 - 1.61$	$0.0 - 1.61$	0.866	0.866	0.866	0.866	0.866	0.866
b_1	0.0109	0.0109	0.0109	0.0109	$0.0 - 0.1$	$0.0 - 0.1$	0.0109	0.0109	0.0109	0.0109
n_U	-	1350	-	1350	-	1350	-	1350	-	1350
d_D	lognormal	lognormal	lognormal	lognormal	lognormal	lognormal	lognormal	lognormal	normal lognormal gamma	normal lognormal gamma
$d_{\overline{D}}$	lognormal	lognormal	lognormal	lognormal	lognormal	lognormal	lognormal	lognormal	normal lognormal gamma	normal lognormal gamma

***Table 3**: The settings of the program 'Bayesian Diagnostic Uncertainty' for the figures 5-19*

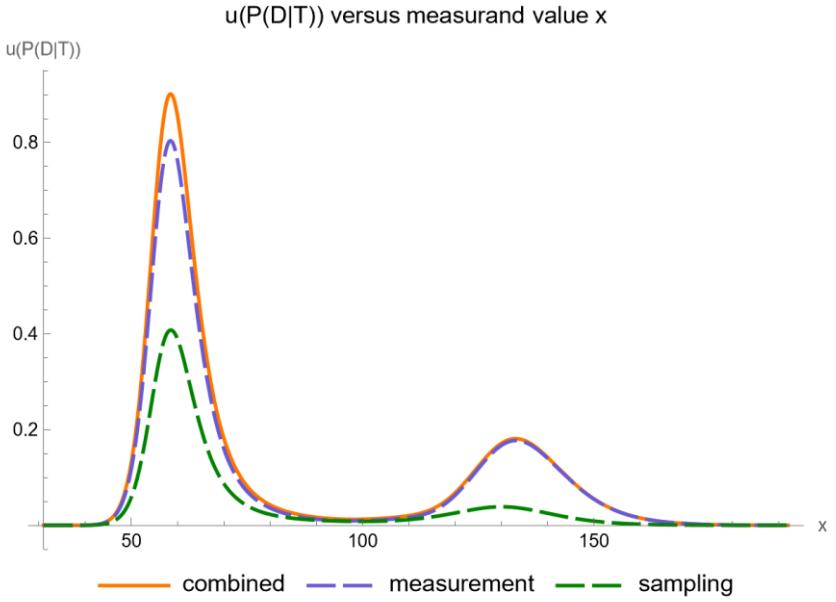

Figure 5. *Standard sampling, measurement, and combined uncertainty of the posterior probability for diabetes versus FPG curve plot, with the settings of the program in Table 2.*

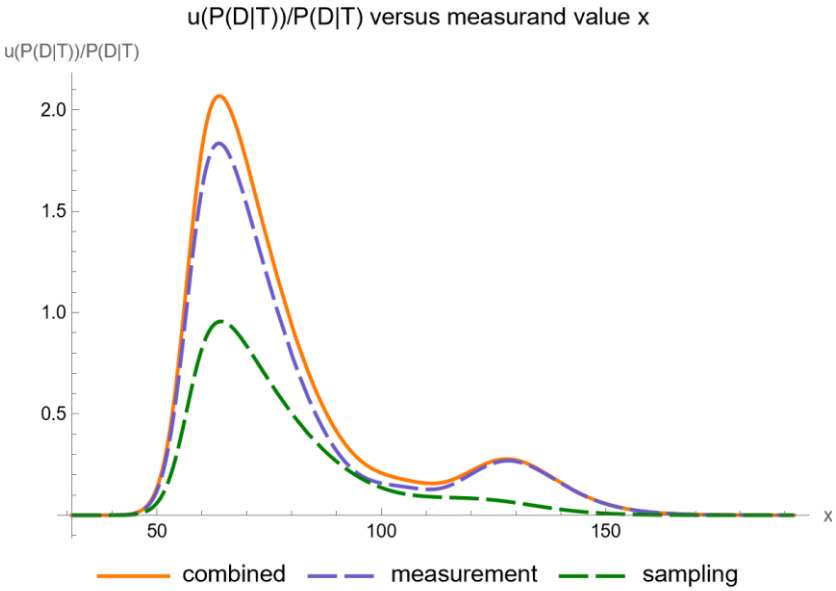

Figure 6. *Relative standard sampling, measurement, and combined uncertainty of the posterior probability for diabetes versus FPG curve plot, with the settings of the program in Table 2.*

Figure 5 shows the plots of the standard sampling, measurement and combined uncertainty of posterior probability for diabetes versus FPG, while Figure 6 shows the respective plots of the relative standard uncertainty.

Figure 7 shows the plots of the confidence intervals of posterior probability for diabetes versus FPG, for a confidence level $p = 0.95$.

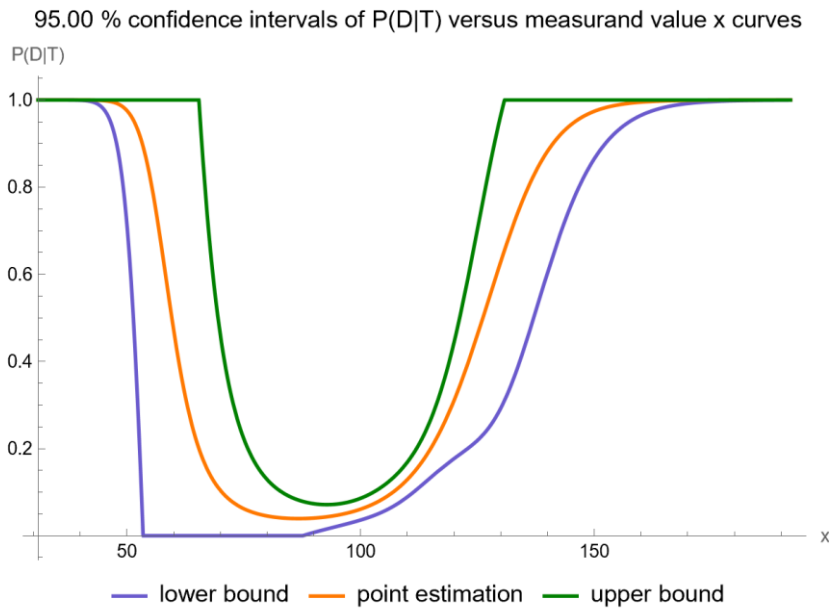

Figure 7. *Confidence intervals of the posterior probability for diabetes versus FPG curves plot, with the settings of the program in Table 2.*

Assessing the combined standard uncertainty of the posterior probability for diabetes, we note the following:

1. It is substantially affected by measurement uncertainty of FPG.
2. Two local maxima are observed, corresponding to the regions near the steepest segments of the posterior probability curve, which exhibits an approximately double sigmoidal configuration. These maxima are quantitatively defined as follows:
   1.1 At an FPG value of 58.7, the posterior probability for disease is equal to 0.585, while the combined standard uncertainty is equal to 0.893.
   1.2 At an FPG value of 133.2, the posterior probability for disease is equal to 0.725, while the combined standard uncertainty is equal to 0.182.

   This pattern of local maxima is indicative of heightened uncertainty in the regions where the posterior probability curve demonstrates its most pronounced inflections. The confidence intervals are affected accordingly.

Figure 8 shows the plots of the standard sampling, measurement, and combined uncertainty of posterior probability for diabetes versus the constant contribution b_0 of measurement uncertainty of FPG, while Figure 9 shows the respective plots of the relative standard uncertainty.

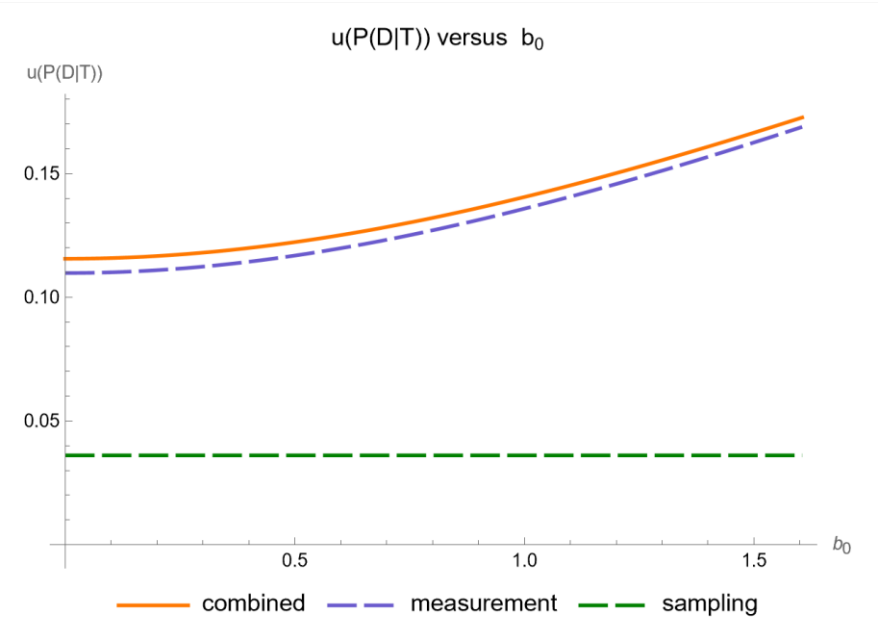

Figure 8. *Standard sampling, measurement, and combined uncertainty of the posterior probability for diabetes versus measurement uncertainty constant contribution b_0 curve plot, with the settings of the program in Table 2.*

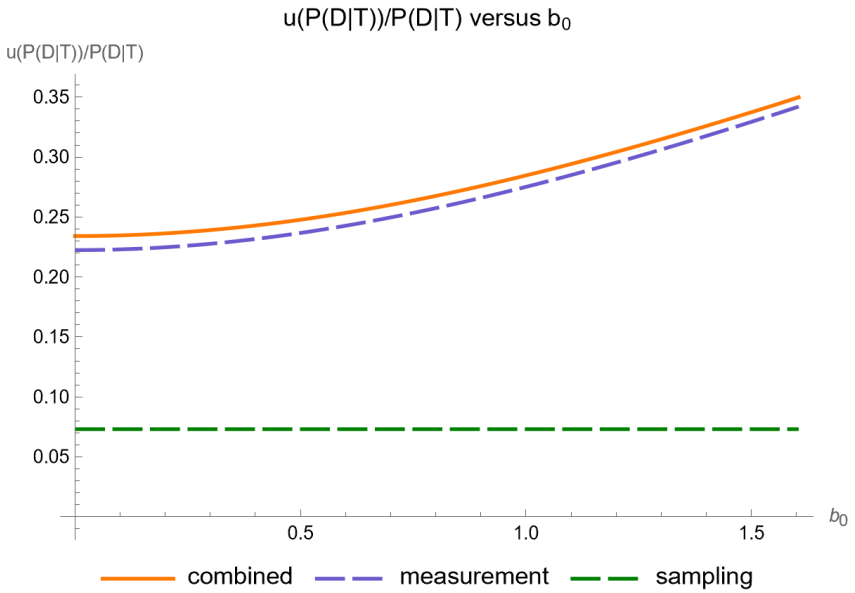

Figure 9. *Relative standard sampling, measurement, and combined uncertainty of the posterior probability for diabetes versus measurement uncertainty constant contribution b_0 curve plot, with the settings of the program in Table 2.*

Figure 10 shows the plots of the confidence intervals of posterior probability for diabetes versus the constant contribution u_0 of measurement uncertainty of FPG, for a confidence level $p = 0.95$.

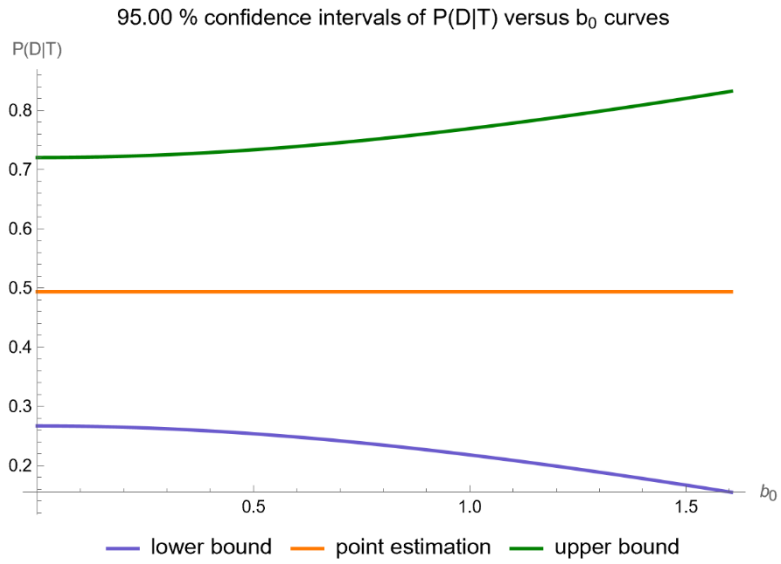

Figure 10. *Confidence intervals of the posterior probability for diabetes versus measurement uncertainty constant contribution b_0 curves plot, with the settings of the program in Table 2.*

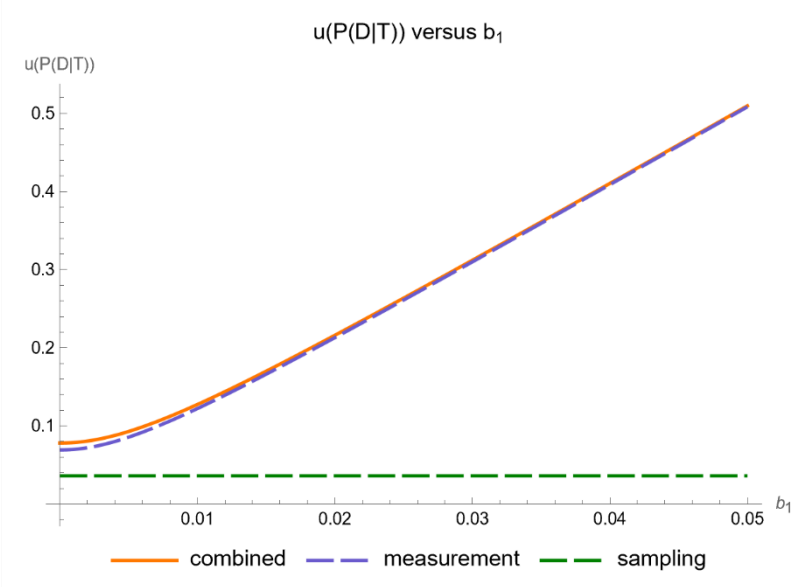

Figure 11. *Standard sampling, measurement, and combined uncertainty of the posterior probability for diabetes versus measurement uncertainty proportionality constant b_1 curve plot, with the settings of the program in Table 2.*

Figure 11 shows the plots of the standard sampling, measurement, and combined uncertainty of posterior probability for diabetes versus the proportionality constant b_1 of measurement uncertainty of FPG, while Figure 12 shows the respective plots of the relative standard uncertainty.

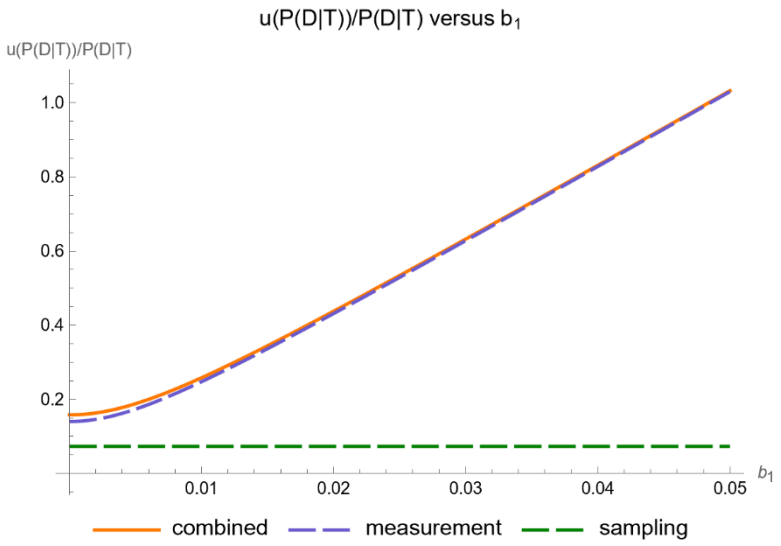

Figure 12. *Relative standard sampling, measurement, and combined uncertainty of the posterior probability for diabetes versus measurement uncertainty proportionality constant b_1 curve plot, with the settings of the program in Table 2.*

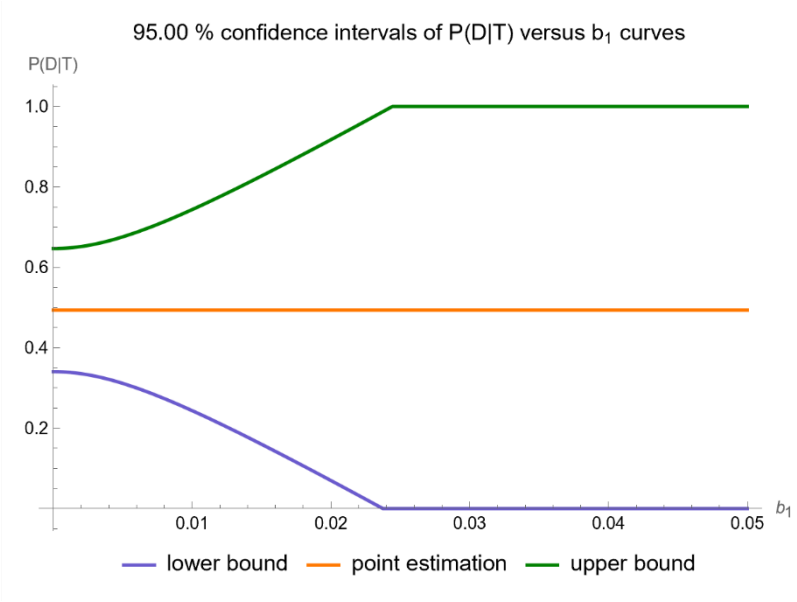

Figure 13. *Confidence intervals of the posterior probability for diabetes versus measurement uncertainty proportionality constant b_1 curves plot, with the settings of the program in Table 2.*

Figure 13 shows the plots of the confidence intervals of posterior probability for diabetes versus the proportionality constant u_1 of measurement uncertainty of FPG, for a confidence level $p = 0.95$.

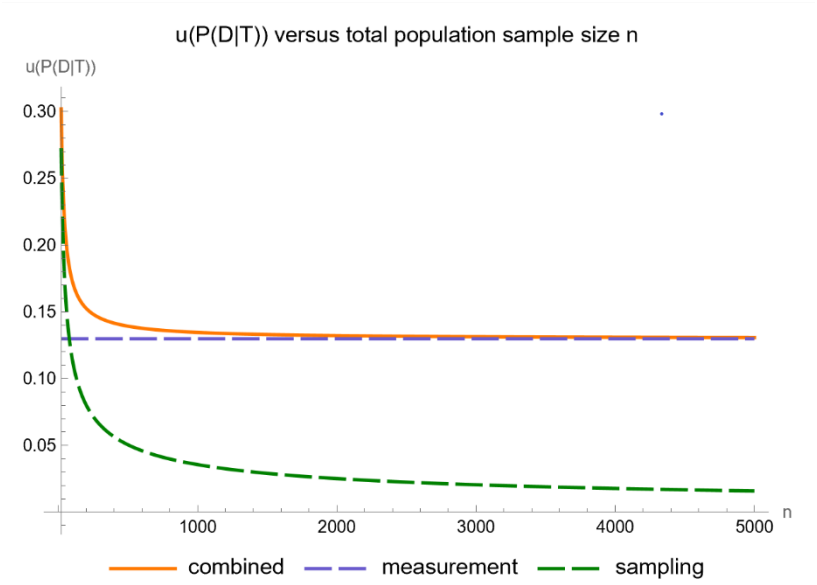

Figure 14. *Standard sampling, measurement, and combined uncertainty of the posterior probability for diabetes versus total population sample size curve plot, with the settings of the program in Table 2.*

Figure 15. *Relative standard sampling, measurement, and combined uncertainty of the posterior probability for diabetes versus total population sample size curve plot, with the settings of the program in Table 2.*

Figure 14 shows the plots of the standard sampling, measurement, and combined uncertainty of posterior probability for diabetes versus the total population size, while Figure 15 shows the respective plots of the relative standard uncertainty.

Figure 16 shows the plots of the confidence intervals of posterior probability for diabetes versus the total population size, for a confidence level $p = 0.95$.

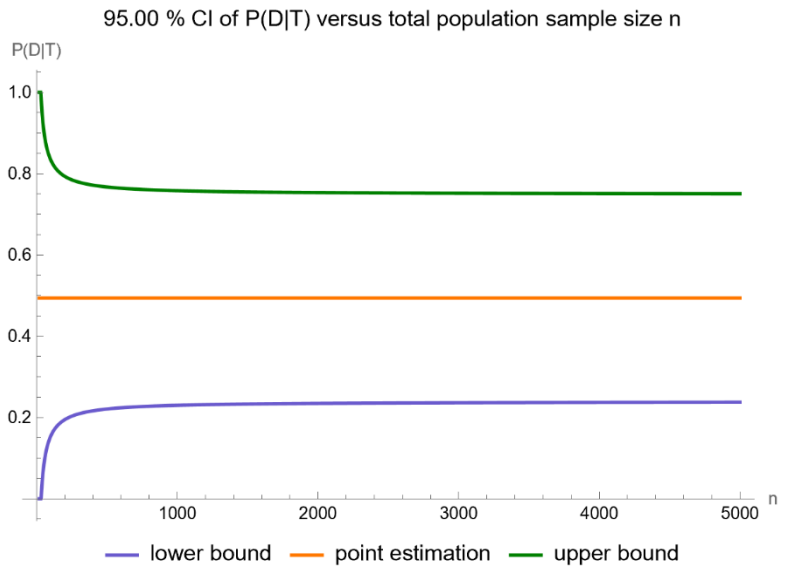

Figure 16. *Confidence intervals of the posterior probability for disease (diabetes) versus total population sample size curve plot curves plot, with the settings of the program in Table 2.*

As anticipated, the impact of sampling uncertainty decreases markedly as the size of the population sample increases.

Figure 17 shows a table of the standard sampling, measurement, and combined standard uncertainty of posterior probability for diabetes for FPG value equal to 126 mg/dl , while Figure 18 shows a table of the respective values of relative standard uncertainty.

standard uncertainty of posterior probability for disease					
measurand distribution		probability	standard uncertainty		
diseased	nondiseased		combined	measurement	sampling
normal	nornal	0.541991	0.170704	0.166022	0.039708
	lognormal	0.508692	0.134128	0.129443	0.035140
	gamma	0.515938	0.145254	0.140599	0.036475
lognormal	nornal	0.526974	0.134704	0.129786	0.036066
	lognormal	0.493604	0.134704	0.129786	0.036066
	gamma	0.500853	0.145916	0.141041	0.037400
gamma	nornal	0.531176	0.171538	0.166723	0.040358
	lognormal	0.497819	0.134538	0.129702	0.035746
	gamma	0.505069	0.145730	0.140933	0.037083

Figure 17. *Table of the standard sampling, measurement, and combined uncertainty of the posterior probability for diabetes , with the settings of the program in Table 2.*

relative standard uncertainty of posterior probability for disease					
measurand distribution		probability	relative standard uncertainty		
diseased	nondiseased		combined	measurement	sampling
normal	nornal	0.541991	0.314958	0.306318	0.073264
	lognormal	0.508692	0.263672	0.254462	0.069079
	gamma	0.515938	0.281533	0.272512	0.070697
lognormal	nornal	0.526974	0.255618	0.246285	0.068441
	lognormal	0.493604	0.272900	0.262936	0.073068
	gamma	0.500853	0.291335	0.281602	0.074673
gamma	nornal	0.531176	0.322940	0.313875	0.075979
	lognormal	0.497819	0.270255	0.260541	0.071806
	gamma	0.505069	0.288535	154.000000	0.073422

Figure 18. *Table of the relative standard sampling, measurement, and combined uncertainty of the posterior probability for diabetes , with the settings of the program in Table 2.*

Figure 18 shows the confidence intervals of posterior probability for diabetes for FPG value equal to 126 mg/dl, for confidence level $p = 0.95$.

posterior probability for disease: 95.00% confidence intervals				
diseased	nondiseased	point estimation	lower bound	upper bound
normal	nornal	0.541991	0.207147	0.876836
	lognormal	0.508692	0.245600	0.771784
	gamma	0.515938	0.231020	0.800856
lognormal	nornal	0.526974	0.262753	0.791196
	lognormal	0.493604	0.229382	0.757825
	gamma	0.500853	0.214638	0.787069
gamma	nornal	0.531176	0.194697	0.867655
	lognormal	0.497819	0.233923	0.761715
	gamma	0.505069	0.219218	0.790920

Figure 19. *Confidence intervals of the posterior probability for disease (diabetes) , with the settings of the program in Table 2.*

The tables distinctly demonstrate the considerable magnitude of uncertainty associated with the posterior probability for diabetes at a FPG level of 126. Furthermore, the posterior probabilities for diabetes delineated in the tables suggest a limited concordance between the classification criteria of diabetes derived from the OGTT and FPG tests [26], as found previously in existing literature [33].

6. Discussion

6.1.Reevaluation of Traditional Diagnostic Methods

Traditional diagnostic methods rely on the use of predetermined thresholds, however, this often fails to consider the complexities of disease pathology. While this has been historically effective, it would appear that it lacks the ability to offer a wholistic approach in today's patient centered medicine, where personalized care is paramount [34]. The evolving nature of diseases and everchanging patient demographics increase the complexity of the diagnostic process, pushing the boundaries of conventional methodologies. In this challenging context, Bayesian inference emerges

as an alternative approach, offering detailed probabilistic evaluations that can adapt to the individual patient profiles [2,3].

Nevertheless, the accurate estimation of uncertainty in posterior probabilities within Bayesian inference remains a critical challenge. This aspect is particularly crucial in diagnostic tests for life-threatening diseases as well as screening tests, where the risks are extremely high. The ability to precisely quantify this uncertainty is not only an academic concern but a practical necessity in improving diagnostic accuracy and patient outcomes.

To address this, our software conducts an in-depth investigation into the sampling, measurement, and combined uncertainty of Bayesian posterior probabilities. This exploration is not only vital for enhancing clinical decision-making but also plays a significant role in the fields of quality and risk management in laboratory medicine [35]. Additionally, it contributes to the design and implementation of clinical studies aimed at evaluating diagnostic tests [36]. As mentioned in the *Introduction* section, despite the extensive body of research on Bayesian diagnosis and uncertainty as separate entities, the intersection of these two areas remains relatively unexplored [37,38].

The illustrative case study, focusing on individuals aged 70 to 80 years, was designed to mitigate age-related variations in disease prevalence. This focus exemplifies the intricate considerations required in modern diagnostics, where factors such as age, genetics, and lifestyle choices should be accounted for in the diagnostic equation.

Our software manages through its rigorous analysis of sampling, measurement, and combined uncertainty (as illustrated in Figures 5, 6, 8, 9, 11, 12, 14, 15, 17, 18), and the corresponding confidence limits (Figures 7, 10, 13, 16), to display its versatility in addressing these diagnostic challenges. The software's user-friendly interface belies the sophistication of its underlying calculations, offering a powerful tool, especially for medical researchers and professionals.

The case study from Section 4 highlights the substantial impact of combined uncertainty on the diagnostic process. This finding emphasizes the predominant role of measurement uncertainty, and thus highlights the challenging path toward enhancing diagnostic accuracy and reliability. By improving the analytical methods of screening or diagnostic tests, the medical community could achieve more accurate diagnosis, leading to more effective and tailored patient care.

Looking ahead, future research should focus on probing the uncertainty of posterior probabilities under a diverse array of clinically relevant parameter settings. This pursuit is essential in navigating the complexities of diagnostic medicine, striving to meet the ever-evolving challenges with innovative solutions and methodologies.

6.2.Limitations and Future Research Directions

This program's limitations, which provide avenues for further research, include:

1. Underlying assumptions:
   1.1. The existence of gold standards in diagnostics.
   1.2. The hypothesis of parametric distribution of measurements or their transformations.
   1.3. The generally accepted bimodality of the measurands.

If these assumptions are not valid, the program may underestimate the standard uncertainty of the posterior probability for disease.

2. The use of first-order Taylor series approximations in uncertainty propagation calculations, where the use of higher-order approximations may provide more accurate estimations.

3. The approximation of the uncertainty of the prior probability for disease using the Agresti-Coull adjusted Waldo interval, despite more accurate methods being available.

While addressing these limitations would increase considerably computational complexity, they represent key areas for future enhancement.

6.3.Case Study Shortcomings

The case study's main limitations include reliance on the OGTT as the reference method for diagnosing diabetes mellitus, despite several factors influencing glucose tolerance. Additionally, the lognormal distributions used only approximate the distributions of the FPG measurements from NHANES datasets, highlighting the need for more flexible statistical models.

6.4.Challenges in Bayesian Analysis for Disease Diagnosis

While Bayesian analysis may be beneficial in medical diagnostics, it poses certain challenges. For instance, the substantial uncertainty of the posterior probability for disease revealed in our study could lead to clinical indecision. Additionally, there is a notable lack of comprehensive statistical research on the distribution of measurands in both diseased and nondiseased populations, hindering further advancements in Bayesian analysis.

6.5.Implications of Incomplete Data

1. *Over-reliance on Prior Probabilities*: Limited empirical data may cause an over-dependence on prior probabilities, leading to distorted posterior probabilities and potentially flawed clinical decisions.
2. *Increased Uncertainty*: Insufficient data amplifies the uncertainty in computed posterior probabilities, which in turn could exacerbate clinical indecision.
3. *Bias Risks*: Unrepresentative datasets could introduce systemic bias, affecting the accuracy of Bayesian calculations.

6.6.Analysis of the Double Sigmoidal Curve in Posterior Probability Estimation and Its Impact on Uncertainty

The posterior probability for disease curve, characterized by a double sigmoidal shape featuring two symmetrical sigmoid functions, presents compelling analytical perspectives in the field of medical diagnostic statistics. This configuration implies that the risk associated with the disease may escalate at both the lower and upper extremes of a given measurand, while a zone of relative safety exists in the intermediate range. Notably, the uncertainty associated with the posterior probability for disease becomes markedly pronounced along the steep segments of the double sigmoidal curve. This heightened uncertainty is attributable to the fact that minor variations in the measurand value can lead to significant alterations in the computed posterior probability.

6.7.Statistical Software Comparison

Our software provides a broad array of parametric plots and comprehensive tables for posterior probability uncertainty analysis, a feature not readily available in major statistical packages without advanced programming.

The program we have developed represents a novel approach to computing and analyzing the uncertainty of Bayesian posterior probabilities in the realm of disease diagnosis. This tool stands out not only for its innovative capabilities in the field of medical diagnostics but also as a significant

educational and research asset. Considering the challenges and complexities outlined in our discussion, this software provides a much-needed solution to the arduous task of navigating the intricacies of diagnostic uncertainties and the nuanced application of Bayesian methods.

7. Conclusion

The program we have developed represents a novel approach to computing and analyzing the uncertainty of Bayesian posterior probabilities in disease diagnosis. This tool stands out not only for its innovative capabilities in the field of medical diagnostics but also as a significant educational and research asset. Considering the challenges and complexities outlined in the discussion section, this software provides a much-needed solution to the arduous task of navigating the intricacies of diagnostic uncertainties of Bayesian methods.
Looking forward, it would seem it is imperative that future research endeavors focus on the empirical validation of this method through comprehensive clinical trials. Such studies would be essential to establish the efficacy and reliability of the program in real clinical settings. Additionally, there is a compelling need to expand the application of this tool across a diverse range of diagnostic modalities. By doing so, the program could address a broader spectrum of diagnostic challenges, further enhancing its utility and impact on the medical field.

The potential of this program seems to be extending beyond its immediate practical applications in medical diagnostics. As an educational resource, it could offer significant opportunities for training and development in medical statistics, particularly in the understanding and application of Bayesian methods. Its user-friendly interface, coupled with the depth of its analytical capabilities, makes it an ideal tool for both aspiring and experienced professionals in the medical community.

In conclusion, the development and refinement of this program are pivotal steps towards navigating the complexities of modern medical diagnostics. Its role in enhancing the precision and adaptability of diagnostic methods, coupled with its educational benefits, positions it as an indispensable tool in the ongoing evolution of medical practice and research.

8. Supplementary Files

8.1 Supplementary File I

BayesianDiagnosticUncertainty.nb: The program as a Wolfram Mathematica Notebook. Available at https://www.hcsl.com/Tools/BayesianDiagnosticUncertainty/BayesianDiagnosticUncertainty.nb

8.2 Supplementary File II

BayesianUncertaintyCalculations.nb: The calculations for the Bayesian posterior probability of disease and its associated standard uncertainty, in a Wolfram Mathematica Notebook. Available at https://www.hcsl.com/Supplements/ SBDU.zip

8.3 Supplementary File III

BayesianDiagnosticUncertaintyInterface.pdf: A brief description of the interface of the program. Available at: https://www.hcsl.com/Documents/BayesianDiagnosticUncertaintyInterface.pdf

9. Institutional Review Board Statement

Data collection was carried out following the rules of the Declaration of Helsinki. The Ethics Review Board of the National Center for Health Statistics approved data collection and posting the data online for public use [39].

10. Informed Consent Statement

Written consent was obtained from each subject participating in the survey.

11. Data Availability Statement

The data presented in this study are available at https://wwwn.cdc.gov/nchs/nhanes/default.aspx (Accessed at 20/12/2023).

12. Conflicts of Interest

The authors declare no conflict of interest.

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14. Appendices

14.1. Appendix I: Formalisms and Notation

Acronyms

PDF: probability density function

FPG: fasting plasma glucose

OGTT: oral glucose tolerance test

NHANES: National Health and Nutrition Examination Survey

Notation

Parameters

n_D : size of diseased population

μ_D: mean of diseased population

σ_D: standard deviation of diseased population

$n_{\bar{D}}$: size of nondiseased population

$\mu_{\bar{D}}$: mean of nondiseased population

$\sigma_{\bar{D}}$: standard deviation of nondiseased population

r : prior probability for disease (prevalence rate)

$u_s(x)$: standard sampling uncertainty of x

$u_m(x)$: standard measurement uncertainty of x

$u_c(x)$: standard combined uncertainty of x

n_U : number of quality control measurements

b_0 : constant contribution to measurement uncertainty

b_1: measurement uncertainty proportionality constant

$\hat{u}$: mean standard measurement uncertainty

p : confidence level

v_{eff} : effective degrees of freedom

Functions

$P(A)$: probability of the event A

$P(A|B)$: conditional probability of the event A given the event B

$\mathcal{L}(\theta|z)$: likelihood function

$F^{-1}(.)$: the inverse function $F(.)$

Bayes Rule

For the purposes of our study, Bayes' rule is formulated as follows:

$$P(D|T) = \frac{P(T|D)P(D)}{P(T)} = \frac{P(T|D)P(D)}{P(T|D)P(D) + P(T|\bar{D})\big(1 - P(D)\big)}$$

where:

$P(D|T)$ represents the posterior probability of having the disease given a test result x.

$P(T|D)$ denotes the likelihood of obtaining the result x.given the presence of the disease.

$P(T|\bar{D})$ denotes the likelihood of obtaining the result x.given the absence of the disease.

$P(D)$ is the prior probability or prevalence r of the disease.

$P(T)$ signifies the overall probability of the result x.

According to Bayes' rule, the posterior probability for disease for a parameter vector $\boldsymbol{\theta}$ is computed as follows:

$$P(D|T) = \frac{\mathcal{L}_D(\boldsymbol{\theta}|x)r}{\mathcal{L}_D(x|\boldsymbol{\theta})v + \mathcal{L}_{\bar{D}}(x|\boldsymbol{\theta})(1-r)} = \frac{f_D(x|\boldsymbol{\theta})r}{f_D(x|\boldsymbol{\theta})r + f_{\bar{D}}(x|\boldsymbol{\theta})(1-r)}$$

where r denotes the prior probability for disease , $\mathcal{L}_D(\boldsymbol{\theta}|x)$ and $f_D(x|\boldsymbol{\theta})$ denote the likelihood function and the PDF in the presence of the disease, while $\mathcal{L}_{\bar{D}}(x|\boldsymbol{\theta})$ and $f_{\bar{D}}(x;\ \boldsymbol{\theta})$ the respective functions in the absence of the disease.

Parametric Distributions

It is assumed that the test results of the diseased or nondiseased populations follow the normal, lognormal or gamma distribution. The domains of random variables for the respective distributions are defined as follows:

1. The domain of a random variable X following a normal distribution is the set of all real numbers, denoting $-\infty < X < \infty$.
2. The domain of a random variable X following a lognormal distribution is the set of all positive real numbers, denoting $0 < x < \infty$.
3. The domain of a random variable X following a gamma distribution is the set of all positive real numbers, denoting $0 < X < \infty$.

Calculations of the posterior probability for disease and its uncertainty

These calculations are displayed in Supplementary file II (Refer to *Section 8.2*).

14.2. Appendix II: Software Availability and Requirements

Program name: *Bayesian Diagnostic Uncertainty*

Version: 1.0.0

Project home page: https://www.hcsl.com/Tools/BayesianDiagnosticUncertainty/ (accessed 18 December 2023)

Available at:
https://www.hcsl.com/Tools/BayesianDiagnosticUncertainty/BayesianDiagnosticUncertainty.nb

Operating systems: Microsoft Windows, Linux, Apple iOS

Programming language: Wolfram Language

Other software requirements:

For running the program and reading the BayesianDiagnosticUncertaintyCalculations.nb file Wolfram Player® is required, freely available at: https://www.wolfram.com/player/ (accessed 18 December 2023) or Wolfram Mathematica®.

System requirements: Intel® i9™ or equivalent CPU and 32 GB of RAM

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14.3. Appendix III: A Note about the Program

About the program controls

The program features an intuitive tabbed user interface, designed to streamline user interaction and facilitate effortless navigation across its multiple modules and sub-modules.

The numerical settings are defined by the user with menus or sliders. Sliders can be finely manipulated by holding down the alt key or opt key while dragging the mouse. They be even more finely manipulated by also holding the *shift* and/or *ctrl* keys.

Dragging with the mouse while pressing the *ctrl*, *alt*, or *opt* keys zooms plots in or out.

Range of input parameters

x: $maximum(\mu_{\bar{D}} - 5\sigma_{\bar{D}}, \mu_D + 5\sigma_{\bar{D}})$

n_D : 2 – 10,000

μ_D: 0.1 – 10,000

σ_D: 0.01 – 1,000

$n_{\bar{D}}$: 2 – 10,000

$\mu_{\bar{D}}$: 0.1 – 10,000

$\sigma_{\bar{D}}$: 0.01 – 1,000

r: 0.010 – 0.500

n_U: 20-10,000

b_0 : 0 $-$ $\sigma_{\bar{D}}$

b_1: 0 $-$ 0.1

p: 0.900 – 0.999

15. Permanent Citation:

Chatzimichail T, Hatjimihail AT. An Analytical Software for Assessing Uncertainty in Bayesian Parametric Diagnosis in Medicine. Technical Report XXVI. Drama: Hellenic Complex Systems Laboratory, 2024. https://www.hcsl.com/TR/hcsltr26/hcsltr26.pdf

16. License

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